Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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

This supplement contains the following items:

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

Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	N/A
Protocol Number:	C4591001
Phase:	1/2

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

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	15 April 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA), nucleoside-modified messenger RNA (modRNA), or self-amplifying messenger RNA (saRNA). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 4 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162a1 (variant RBL063.3): a uRNA encoding the RBD;

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S;

BNT162c2 (variant RBP020.3): an saRNA encoding the RBD.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and potential efficacy of these 4 prophylactic BNT162 vaccines against COVID-19.

It is expected that the various candidate vaccines may not all be available from the start of the study, in which case they will be rolled into the study in a consecutive fashion as they are released. A Phase 1/2 study of the same vaccine candidates (BNT162-01), conducted in Germany by BioNTech in adults 18 to 55 years of age, is planned to start in April 2020. Study C4591001 is designed to complement and expand upon the German study and confirm the optimal vaccine candidate(s) (BNT162a1, BNT162b1, BNT162b2, or BNT162c2), dose level(s), number of doses, and schedule of administration.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	

Objectives	Estimands	Endpoints
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2–specific WT serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from rise from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2–specific WT serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – infection rate ratio) [ratio of active vaccine to placebo]	• SARS-CoV-2–specific WT serum neutralizing titers • SARS-CoV-2-spike protein–specific binding antibody levels • SARS-CoV-2 RBD–specific binding antibody levels COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

Overall Design

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

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule

- At up to 3 different dose levels

- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

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

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3: a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

Number of Participants

Each group in Stage 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

Each group in Stage 2 will comprise 225 participants (180 receiving active vaccine and 45 receiving placebo). The total number of participants to be enrolled in this stage depends on the number of groups to be pursued.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study may evaluate single-dose and 2-dose (separated by 21 or 60 days) schedules of 3 different dose levels of 4 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 3 µg, 10 µg, 30 µg

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 100 µg

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 100 µg

- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 3 µg, 10 µg, 30 µg

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

Data Monitoring Committee or Other Independent Oversight Committee

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

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

Statistical Methods

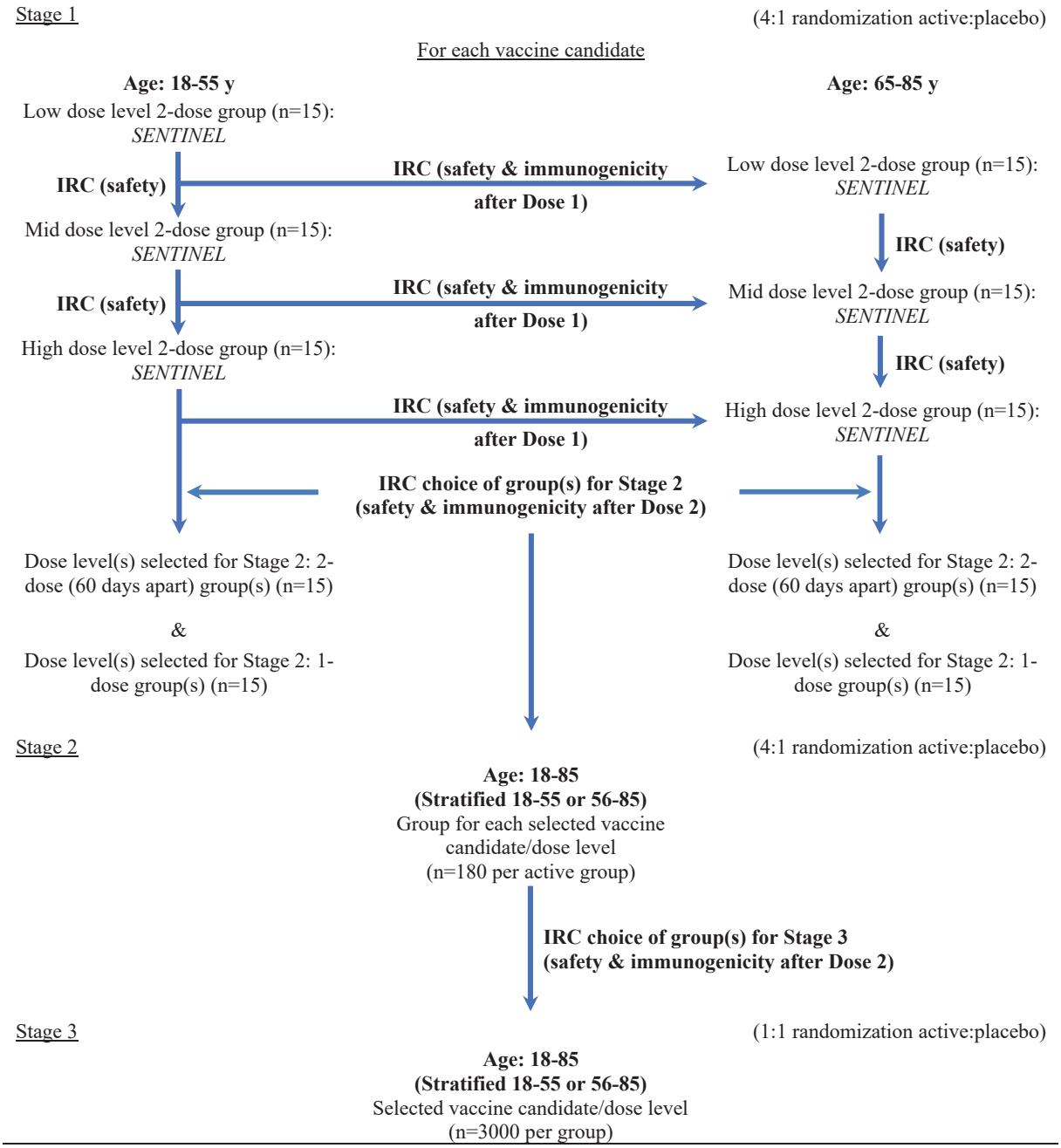
The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. For the third stage, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group, based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

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

The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2–specific WT serum neutralizing titers, SARS-CoV-2-spike protein–specific binding antibody levels, and RBD-specific binding levels at the various time points.

For the secondary efficacy objective, VE is defined as VE = 100 × (1 – IRR), where IRR is the infection rate ratio, the calculated ratio of COVID-19 incidence in the active vaccine group to the incidence in the placebo group. The null hypothesis (VE ≤ 20%) will be rejected if the lower bound of the 95% CI for VE is >20%; no interim analysis of VE is planned.

1.2. Schema



Abbreviation: IRC = internal review committee.

1.3. Schedule of Activities

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

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

1.3.1. Stage 1 Sentinel Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[a]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[b]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[c]		X			X								
Provide participant with 7-day e-diary, thermometer, and measuring device		X			X								
Review e-diary data (daily review is optimal during the active diary period)		◄———	———	———►	◄———	———►							
Review ongoing e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 14 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**154 to 168 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect e-diary or assist the participant to delete application							X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

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

a. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
b. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
c. The first 5 participants in in each sentinel group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.

1.3.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 7 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform physical examination	X								
Measure vital signs	X								
Perform urine pregnancy test (if appropriate)	X	X							
Collect nonstudy vaccine information	X	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Confirm eligibility	X	X							
Measure temperature (body)	X	X							
Review temporary delay criteria	X	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X					
Obtain randomization number and study intervention allocation	X								

Visit Number	1	2	3	4	5	6	7	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**12 to 16 Days After Visit 2**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X						X	
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X							
Review e-diary data (daily review is optimal during the active diary period)	←→	←→							
Review ongoing e-diary symptoms and obtain stop dates		X	X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X						
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)								X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule for the assigned group.

1.3.3. Stage 3 Cohort(s)

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform physical examination	X							
Measure vital signs	X							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Measure temperature (body)	X	X						
Review temporary delay criteria	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Obtain randomization number and study intervention allocation	X							
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL		~50 mL	~50 mL		~50 mL
Obtain nasal (midturbinate) swab	X	X					X	

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Safety Telephone Contact**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Telehealth Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1 or 56 to 70 Days After Visit 1[a]**	**28 to 35 Days After Visit 2**	**154 to 168 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Provide participant with 7-day e-diary, thermometer, and measuring device	X	X						
Review e-diary data (daily review is optimal during the active diary period)	⟷	⟷						
Review ongoing e-diary symptoms and obtain stop dates		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application			X					
Telephone contact				X				
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviation: e-diary = electronic diary.

a. The window for Visit 2 is dependent on the dosing schedule(s) selected for the Stage 3.

2. INTRODUCTION

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

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and potential efficacy of 4 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

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

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

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

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

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Four SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats will be evaluated in this study. Each vaccine candidate is based on 1 of 3 RNA platforms: unmodified messenger RNA (uRNA), nucleoside-modified messenger RNA (modRNA), or self-amplifying messenger RNA (saRNA). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor binding domain (RBD) (version 5). The 4 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162a1** (variant RBL063.3): non–nucleoside-modified uridine-containing messenger RNA (uRNA) with high intrinsic adjuvanticity, encoding the RBD.
- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above but encoding P2 S.
- **BNT162c2** (variant RBP020.3): self-amplifying messenger RNA (saRNA) encoding the RBD, in which higher amounts of protein per injected RNA template can be produced.

2.2.1. Clinical Overview

BNT162 vaccines have not been administered to humans before and thus there are no previous clinical data with these specific vaccines. However, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines are expected to have a favorable safety profile with mild, localized, and transient effects.

2.3. Benefit/Risk Assessment

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

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of an e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel-cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The study design includes the use of sentinel cohorts and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC and DMC will also review safety data throughout the study. Stopping rules are also in place for sentinel cohorts. The first 5 sentinel cohort participants in each group will be observed for 4 hours after vaccination to assess any immediate AEs.
Potential for COVID-19 disease enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	The study excludes participants with likely previous or current COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2–specific WT serum neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

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

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts:*** 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts:*** 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 ***Stage 3 Cohort(s):*** 1, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2–specific WT serum neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2–specific WT serum neutralizing titers to the geometric mean of SARS-CoV-2–specific binding antibody levels at each time point	• SARS-CoV2–specific WT serum neutralizing titers • SARS-CoV-2-spike protein–specific binding antibody levels • SARS-CoV-2 RBD–specific binding antibody levels
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – infection rate ratio) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19 • Symptomatic SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection		Nonvaccine antigen SARS-CoV-2 antibody levels

4. STUDY DESIGN

4.1. Overall Design

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

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule
- At up to 3 different dose levels
- In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])

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

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (Section 1.2).

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

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

4.1.1. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 1.

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see Section 8.2)
- Controlled enrollment:
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level

Groups of participants 65 to 85 years of age will not be started until safety and immunogenicity data for the same vaccine candidate/dose level have been deemed acceptable in the 18- to 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into Stage 2, for each age cohort, 2 additional groups will be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21
- A 1-dose group

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

4.1.2. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 or 56 to 85 years. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- to 55-year and 65- to 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

4.1.3. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 group may be selected to proceed into Stage 3. Participants in this stage will be 18 to 85 years of age, stratified equally: 18 to 55 years or 56 to 85 years. As in Stage 2, it is possible that the 2 age strata may not start concurrently.

The vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

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

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences respiratory symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

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

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data are not currently available to experimentally validate the dose selection and initial starting dose. Therefore, the planned starting doses of 3 µg (for BNT162a1 and BNT162c2) and 10 µg (for BNT162b1 and BNT162b2) in this study are based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components (uRNA, modRNA, saRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it is expected that doses in the 1- to 5-µg range will be immunogenic and induce neutralizing antibodies; however, it is anticipated that 3- to 10-fold higher doses will likely

be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it is expected that doses of up to 100 µg will be well tolerated.

Taken together, the planned starting doses in this study in healthy participants are considered to be safe, but still sufficient to induce an antiviral immune response.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or 18 and 85 years, inclusive, at randomization (dependent upon study stage).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

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

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

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Informed Consent:

4. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

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

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

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

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

5. **Stages 1 and 2 only:** Previous clinical or microbiological diagnosis of COVID-19.

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

    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma
    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - BMI >30 kg/m^2
    - Anticipating the need for immunosuppressive treatment within the next 6 months

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

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

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

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

11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.

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

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

Prior/Concurrent Clinical Study Experience:

15. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

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

Diagnostic Assessments:

17. **Sentinel participants in Stage 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.

18. **Sentinel participants in Stage 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.

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

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

20. **Sentinel participants in Stage 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.4. Screen Failures

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

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

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

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

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:

    - New or increased cough;
    - New or increased shortness of breath;
    - New or increased sore throat;
    - New or increased wheezing;
    - New or increased sputum production;
    - New or increased nasal congestion;
    - New or increased nasal discharge;
    - Loss of taste/smell.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

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

The study may evaluate 2-dose (separated by 21 or 60 days) and single-dose schedules of 3 different dose levels of 4 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]). These 4 investigational RNA

vaccine candidates, with the addition of saline placebo, are the 5 potential study interventions that may be administered to a study participant:

- BNT162a1 (RNA-LNP vaccine utilizing uRNA and encoding the RBD): 3 µg, 10 µg, 30 µg
- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 30 µg, 100 µg
- BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA and encoding the RBD): 3 µg, 10 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

A list of all potential groups in the Stage 1 are shown in Table 1. Each of these groups may or may not progress to the later stages of the study.

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
a-3-2-Y (Sentinel) [uRNA 3 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	3 µg	(n=12) (n=3)	BNT162a1 Placebo	3 µg	(n=12) (n=3)
a-10-2-Y (Sentinel) [uRNA 10 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	10 µg	(n=12) (n=3)	BNT162a1 Placebo	10 µg	(n=12) (n=3)
a-30-2-Y (Sentinel) [uRNA 30 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	30 µg	(n=12) (n=3)	BNT162a1 Placebo	30 µg	(n=12) (n=3)
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
c-3-2-Y (Sentinel) [saRNA 3 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	3 µg	(n=12) (n=3)	BNT162c2 Placebo	3 µg	(n=12) (n=3)
c-10-2-Y (Sentinel) [saRNA 10 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	10 µg	(n=12) (n=3)	BNT162c2 Placebo	10 µg	(n=12) (n=3)
c-30-2-Y (Sentinel) [saRNA 30 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	30 µg	(n=12) (n=3)	BNT162c2 Placebo	30 µg	(n=12) (n=3)
a-3-2-O (Sentinel) [uRNA 3 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	3 µg	(n=12) (n=3)	BNT162a1 Placebo	3 µg	(n=12) (n=3)
a-10-2-O (Sentinel) [uRNA 10 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	10 µg	(n=12) (n=3)	BNT162a1 Placebo	10 µg	(n=12) (n=3)
a-30-2-O (Sentinel) [uRNA 30 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	30 µg	(n=12) (n=3)	BNT162a1 Placebo	30 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
c-3-2-O (Sentinel) [saRNA 3 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	3 µg	(n=12) (n=3)	BNT162c2 Placebo	3 µg	(n=12) (n=3)
c-10-2-O (Sentinel) [saRNA 10 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	10 µg	(n=12) (n=3)	BNT162c2 Placebo	10 µg	(n=12) (n=3)
c-30-2-O (Sentinel) [saRNA 30 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	30 µg	(n=12) (n=3)	BNT162c2 Placebo	30 µg	(n=12) (n=3)
Single-Dose Groups			**Day 1**			**Day 22**		
a-x-1-Y [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-Y [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
a-x-1-O [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-O [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
a-x-2L-Y [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-Y [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)
a-x-2L-O [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-O [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; saRNA = self-amplifying messenger ribonucleic acid; TBD = to be determined; uRNA = uridine-containing messenger ribonucleic acid.

6.1. Study Intervention(s) Administered

Intervention Name	BNT162a1 (BNT 162 RNA-LNP vaccine utilizing uRNA)	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162c2 (BNT162 RNA-LNP vaccine utilizing saRNA	Saline placebo
Type	Vaccine	Vaccine	Vaccine	Vaccine	Placebo
Dose Formulation	uRNA	modRNA	modRNA	saRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)	3-, 10-, 30-µg	10-, 30-, 100-µg	10-, 30-, 100-µg	3-, 10-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

6.1.1. Administration

Participants will receive 1 dose (0.5 mL) of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Stage 1 sentinel cohort participants, Visits 1 and 2 for all other participants) in accordance with the study's SoA.

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

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

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

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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

6.3.2. Blinding of Site Personnel

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

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

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Stage 1 and in Stage 2. Sponsor staff will be blinded to study intervention allocation in Stage 3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). Unblinded clinician(s) who are not direct members of the study team will review unblinded protocol deviations.

6.3.4. Breaking the Blind

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

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

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

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

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

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

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

6.5.1. Prohibited During the Study

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

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

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

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Stage 1 sentinel cohorts, Visit 4 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 3 for Stage 3 participants).

Receipt of blood/plasma products or immunoglobulins within 6 months before enrollment through conclusion of the study.

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

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

6.5.2. Permitted During the Study

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

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

Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

Individual participant dose modifications will not be made in this study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

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

The total blood sampling volume for individual participants in this study is approximately 530 mL for participants in the Stage 1 sentinel cohorts; 350 mL for participants in the Stage 1 nonsentinel cohorts and Stage 2 participants; and 200 mL for Stage 3 participants. Additionally, 50 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, a telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. Four definitions of potential SARS-CoV-2–related cases will be considered:

- Centrally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and SARS-CoV-2 NAAT positive at central laboratory
- Locally confirmed COVID-19: presence of at least 1 symptom described in Section 8.13 and investigator-confirmed SARS-CoV-2 NAAT positive at a local testing facility
- Centrally confirmed symptomatic seroconversion to SARS-CoV-2 (exploratory): presence of at least 1 symptom described in Section 8.13 and a positive nonvaccine antigen SARS-CoV-2 antibody result in a participant whose most recent prior nonvaccine antigen SARS-CoV-2 antibody result was negative
- Centrally confirmed asymptomatic seroconversion to SARS-CoV-2 (exploratory): positive nonvaccine antigen SARS-CoV-2 antibody result in a participant with a prior nonvaccine antigen SARS-CoV-2 antibody result was negative

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

- SARS-CoV-2–specific WT serum neutralization assay
- SARS-CoV-2-spike (S) protein–specific IgG direct Luminex immunoassay
- SARS-CoV-2 RBD–specific IgG direct Luminex immunoassay

- Nonvaccine antigen (NVA) Ig direct Luminex immunoassay. The NVA will include a SARS-CoV-2 target antigen that is not derived from the S glycoprotein, most likely an antigen derived from the SARS-CoV-2 nucleoprotein.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

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

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

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

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

The safety parameters also include e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments (Sentinel-Cohort Participants Only)

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

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

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

8.2.2. Electronic Diary

Participants will be required to complete an e-diary through an application installed on a provisioned device or on the participant's own personal device. The participant will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

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

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

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

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

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

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 2.

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

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.2.3. Systemic Events

During the e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

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

Table 3. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the e-diary in the evening daily during the e-diary reporting period. It will also be collected at any time during the e-diary data collection periods when fever is suspected. Fever is

defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

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

Table 4. Scale for Fever

38.0-38.4°C (100.4-101.1°F)
38.5-38.9°C (101.2-102.0°F)
39.0-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.2.2.5. Antipyretic Medication

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

8.2.3. Stopping Rules

The following stopping rules are in place for all Stage 1 sentinel-cohort participants, based on review of AE data and e-diary reactogenicity data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

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

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

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.

- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

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

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

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

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

2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event within 7 days after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement within 7 days after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) within 21 days after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

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

8.2.3.1. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study during Stages 1 and 2, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment.

Participants in all stages of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see Section 8.13). All NAAT-confirmed cases will be reviewed contemporaneously by the IRC and the DMC (see Section 9.6). In addition, instances of symptomatic and asymptomatic seroconversion to SARS-CoV-2 (see Section 8.1) will be reviewed.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review. Since the DMC is able to review unblinded information, it will also be able to compare cases in active vaccine and placebo recipients in Stage 3 (when sponsor staff will be blinded).

8.2.5. Pregnancy Testing

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

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Stage 1 sentinel-cohort participants, Visit 4 for Stage 1 nonsentinel participants and Stage 2 participants, and Visit 3 for Stage 3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-cohort participants, Visit 5 for Stage 1 nonsentinel cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical

History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccines SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a

follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

CRF. However, a copy of the completed Vaccines SAE Report Form is maintained in the investigator site file.

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Medication Errors

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

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

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;

- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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

In the event of a medication dosing error, the sponsor should be notified immediately.

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

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

8.4. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

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

8.11. Study Procedures

8.11.1. Stage 1 Sentinel Cohorts

8.11.1.1. Screening: (0 to 14 Days Before Visit 1)

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

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

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.

- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 20 mL) for serological assessment of prior COVID-19 infection.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

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

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

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

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

- Record AEs as described in Section 8.3.

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).

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

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

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

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

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

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

- The first 5 participants vaccinated in each Stage 1 sentinel group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

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

- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

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

- Record AEs as described in Section 8.3.

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

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

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

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

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

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

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

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

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Perform physical examination including vital signs (body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts

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

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

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

- Obtain a nasal (midturbinate) swab (collected by site staff).

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

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

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

- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule for the assigned group.

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

- Record AEs as described in Section 8.3.

- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

- Measure the participant's body temperature.

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

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

- Obtain a nasal (midturbinate) swab (collected by site staff).

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

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 2-Week Follow-up Visit: (12 to 16 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.5. Visit 5 – 6-Month Follow-up Visit: (154 to 168 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.7. Visit 7 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3. Stage 3 Cohort(s)

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

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

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.2. Visit 2 – Vaccination 2: (19 to 23 Days or 56 to 70 Days After Visit 1)

The window for Visit 2 is dependent on the dosing schedule(s) selected for Stage 3.

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

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and potential efficacy (see Section 7.1).

- Measure the participant's body temperature.

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

- Obtain a nasal (midturbinate) swab (collected by site staff).

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

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.3.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.11.3.4. Visit 4 – 6-Month Safety Telephone Contact: (154 to 168 Days After Visit 2)

- Contact the participant by telephone in order to obtain the following information.
- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.3.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).

- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. Note that this does not substitute for a participant's routine medical care. Therefore participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;
- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

8.13.1. Potential COVID-19 Illness Telehealth Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This telehealth visit is expected to involve the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several telehealth contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory. The result from this swab will be provided to the site once it is available, but this will not be in real time, and cannot be relied upon to direct clinical care. Therefore, the participant should be encouraged to seek care, if appropriate, from his or her usual provider.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms
    - Clinical diagnosis
    - Local laboratory COVID-19 test result
    - Full blood count
    - C-reactive protein
    - Number and type of any healthcare contact; duration of hospitalization and intensive care unit stay
    - Need for oxygen therapy
    - Need for ventilation
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

At the end of Stage 3, the vaccine efficacy (VE) will be evaluated. VE is defined as VE = 100 × (1 – IRR), where IRR is the infection rate ratio, the calculated ratio of the COVID-19 infection rate in the active vaccine group to the incidence rate in the placebo group. The efficacy hypothesis is:

H_0: VE ≤20% vs H_a: VE >20%

where H_0 and H_a represent null hypothesis and alternative hypothesis. For participants with multiple infections, only the first infection will contribute to the VE calculation in the hypothesis test.

The efficacy will be demonstrated if the null hypothesis VE ≤20% is rejected at the 0.025 significance level, that is, when the lower limit of the 2-sided 95% CI for VE is >20%, which is derived using the Clopper-Pearson method as described by Agresti.[9]

9.2. Sample Size Determination

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 56 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 840 participants. Stage 2 will include 1 or more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, for the selected vaccine candidate/dose level, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group (1:1 randomization ratio), based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000
0.10%	0.01	0.04	0.16	0.95
0.50%	0.06	0.20	0.59	>0.99
1.00%	0.11	0.36	0.84	>0.99
2.00%	0.22	0.60	0.97	>0.99
3.00%	0.31	0.75	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who are 18 to 85 years of age (stratified by 18 to 55 and 56 to 85) (inclusive) on the day of first vaccination, receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who are 18 to 85 years of age (stratified by 18 to 55 and 56 to 85) (inclusive) on the day of first vaccination, receive 2 randomized vaccinations within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result 21 days after Dose 1.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result 14 days after Dose 2.

Population	Description
Evaluable efficacy	All eligible randomized participants who are 18 to 85 years of age (inclusive) on the day of first vaccination, receive 2 vaccinations as randomized within the predefined window, have the efficacy measurement after Dose 2, and have no other major protocol deviations as determined by the clinician.
All-available efficacy	All eligible randomized participants who are 18 to 85 years of age (inclusive) on the day of first vaccination, receive at least 1 vaccination, and have the efficacy measurement after Dose 2.
Safety	All randomized participants who receive at least 1 dose of the study intervention and have safety data assessed after any dose.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product (active/placebo) within each group before vaccination and at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 Geometric means and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. **GMFRs of SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific antibody levels and RBD-specific binding levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back

Endpoint	Statistical Analysis Methods
	to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. **Percentage of participants with ≥4-fold rise in SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific antibody levels and RBD-specific binding levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 cohort(s): 1, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2–specific WT serum neutralizing titer fold rise to SARS-CoV-2-spike protein–specific antibody and SARS-CoV-2 RBD–specific binding antibody** For SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific binding antibody levels and RBD-specific binding antibody levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2 • Stage 3 Cohort(s): 1, 12, and 24 months after Dose 2

Endpoint	Statistical Analysis Methods
	GMRs will be limited to participants with nonmissing values for both SARS-CoV-2–specific WT serum neutralizing titers and SARS-CoV-2-spike protein–specific antibody/SARS-CoV-2 RBD–specific binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2–specific WT serum neutralizing titers minus SARS-CoV-2-spike protein–specific antibody for each participant) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale. The same analysis methods will be applied to the immunogenicity endpoints in Stages 2 and 3. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Tertiary/ exploratory immunogenicity	**Correlation of an RT-PCR–confirmed COVID-19 infection and seropositivity/seroconversion measured by nonvaccine antigen SARS-CoV-2 antibody** If sufficient data are collected, percentages (and 2-sided 95% CIs) of participants with confirmed COVID-19 and nonvaccine antigen SARS-CoV-2 antibody levels after Dose 1 and after Dose 2 will be provided. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2–specific WT serum neutralizing titers, SARS-CoV-2-spike protein–specific antibody, and RBD-specific binding antibody after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The statistical analysis of efficacy will be based on the evaluable efficacy population (primary analysis) and the all-available efficacy population as defined in Section 9.3.

Endpoint	Statistical Analysis Methods
Secondary efficacy	**Ratio of COVID-19 incidence per 1000 person-years of follow-up for the active vaccine group to the placebo group** Vaccine efficacy will be estimated by 100 × (1 – IRR), where IRR is the infection rate ratio, the calculated ratio of COVID-19 infection incidence per 1000 person-years follow-up in the active vaccine group to the corresponding incidence in the placebo group after 2 doses. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. For the primary analysis, missing efficacy data will not be imputed. A sensitivity analysis may be performed by imputing missing values; details will be provided in the SAP.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • For Stage 1 sentinel cohorts, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. • AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is

Endpoint	Statistical Analysis Methods
	defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. • Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. • SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after last dose will be provided for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
Exploratory	• N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2–specific WT serum neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the SARS-CoV-2 spike protein–specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the SARS-CoV-2 RBD–specific binding antibody level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

9.5. Interim Analyses

No formal interim analysis is planned in this study. As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 2.
- Complete safety, immunogenicity, and efficacy analysis after complete data are available for all participants for Stage 3.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC and a DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC will include:

- Review of safety data to permit dose escalations
- Review of safety data in the case of a stopping rule being met
- Review of safety and immunogenicity data to:
    - Allow groups of participants of 65 to 85 years of age to proceed
    - Select vaccine candidate(s)/dose level(s), and schedule(s) to proceed into Stage 2
    - Select vaccine candidate(s)/dose level(s), and schedule(s) to proceed into Stage 3
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
    - Whether any groups may not be started
    - Whether any groups may be terminated early

  - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule

- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule

- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 6).

Table 6. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0

Table 6. Laboratory Abnormality Grading Scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccines SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccines SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccines SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccines SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and EDP supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccines SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccines SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form
• Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;
    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use application
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer

Abbreviation	Term
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	infection rate ratio
IRT	interactive response technology
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein

Abbreviation	Term
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	uridine-containing messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

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

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

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

Protocol Amendment Summary of Changes Table

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

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

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations. • Added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of the active safety surveillance period. • Added corresponding exploratory objectives and statistical analysis details. • Removed immunogenicity analyses of titers greater than defined threshold(s). • Removed the need for blinded COVID-19 case review after the final efficacy analysis. • Included the possibility, due to local circumstances related to the COVID-19 pandemic, that study procedures that do not require in-person participant contact may be performed by telehealth. • In light of additional information to better estimate the standard deviation of SARS-CoV-2

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

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified that premenarchal females are not WOCBP. • Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2." • Clarified the degree of unblinding on the unblinded submissions team in Section 6.3.3. • Made provision for a second dose of BNT162b2 in participants who were affected by a medication error at Visit 2 in Section 6.6. • Provided further clarification regarding discontinuation of study intervention in Section 7.1. • Modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Added that 2 periods of potential COVID-19 symptoms within 4 days will be considered as a single illness. • Provided guidance in Section 8.13 regarding circumstances in which a SARS-CoV-2 test might be required even if symptoms within 7 days following each vaccination are considered more likely due to vaccine reactogenicity. • Made allowance in Section 8.13 for a second SARS-CoV-2 test to be performed within the same potential COVID-19 illness if it is in accordance with routine practice. • Added Section 8.15 to describe the reporting of SARS-CoV-2 test results and their implications for participants receiving a second vaccine dose. • Added statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age.

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

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

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

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year age cohort and advancement to groups of participants 65 to 85 years of age

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition: • Removed hemoglobin change-from-baseline abnormalities from the laboratory abnormality grading scale as abnormalities should be graded based upon absolute values
Protocol amendment 1	13 May 2020	• Following regulatory feedback: • Modified exclusion criteria and prohibited inhaled/nebulized corticosteroids for sentinel participants in Stage 1 • Clarified that the rapid test for prior COVID-19 infection for sentinel participants in Stage 1 will be used only for screening purposes • Removed time frames for stopping rules • Stated that data supporting the selection of vaccine candidate(s)/dose level(s) and schedule(s) for Stages 2 and 3 will be submitted to the FDA for review • Following preliminary experience in the BioNTech study conducted in Germany (BNT162-01): • Decreased the dose levels for BNT162a1 and BNT162c2 Additionally: • Clarified the roles of BioNTech and Pfizer • Amended text so that the IRC decision to progress group(s) into Stages 2 and 3 can be based upon safety and immunogenicity data after Dose 1 or 2 • Clarified safety data requirements to permit dose escalation • Amended text so that the progression to participants 65 to 85 years of age can be based upon data from the same RNA platform • Incorporated a protocol administrative change to correct the variant designation and the encoded antigen to BNT162c2 • Clarified that the SARS-CoV-2 neutralizing assay does not employ wild-type virus • Clarified that the SARS-CoV-2 spike protein–binding antibody assay is specific for the S1 subunit • Clarified that efficacy against COVID-19 is based upon illness (not infection) rate ratio • Incorporated a protocol administrative change to state that the study placebo may be supplied in a glass or plastic vial

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Corrected a typographical error in Section 6.5.1 regarding the time frame for prior receipt of blood/plasma products or immunoglobulins • Corrected a typographical error in Table 2 regarding the lower limit of diameter (cm) for mild redness and swelling • Updated the °C fever scale in Table 4 to ensure that all potential °F values are correctly assigned • Incorporated a protocol administrative change to clarify that a rapid test for prior COVID-19 infection will be performed for sentinel participants in Stage 1, and a serum sample will be drawn for potential future assessment • Clarified that, after screening, physical examinations in sentinel participants in Stage 1 will be directed • Clarified the descriptions of the populations for analysis to align with the statistical analysis plan • Added a complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3 • Amended text so that the stopping rules apply to an RNA platform rather than a specific vaccine candidate
Original protocol	15 April 2020	N/A

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

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

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

Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers

Objectives	Estimands	Endpoints
	• Geometric mean concentrations (GMCs) at each time point • GMFR from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

For Phase 2/3

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

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

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

Objectives[a]	Estimands	Endpoints
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers

Objectives[a]	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for a description of the manufacturing process.

Overall Design

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

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

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

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

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

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

Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

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

Number of Participants

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

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

Intervention Groups and Duration

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

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg

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

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

Data Monitoring Committee or Other Independent Oversight Committee

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

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

Statistical Methods

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

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

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

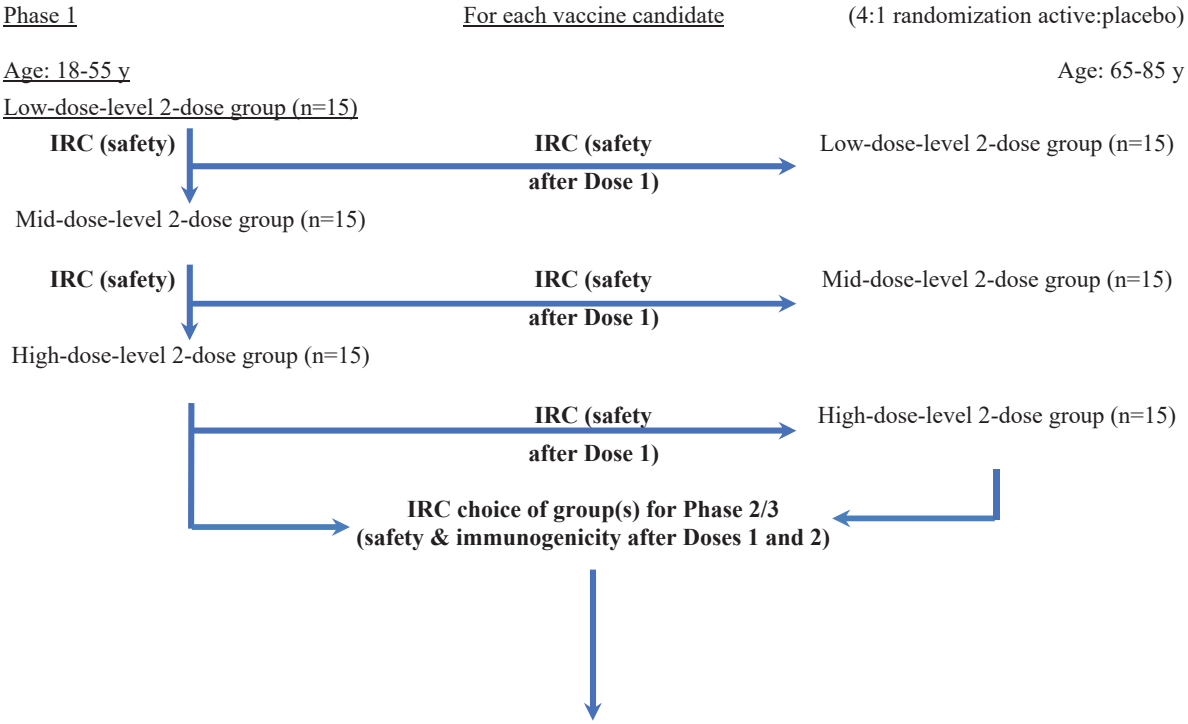
The secondary objectives regarding VE against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated. VE will be demonstrated if the lower bound of the 95% CI for VE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

In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

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

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥4-fold rise, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, full-length S-binding or S1-binding IgG levels, and/or RBD-binding IgG levels (Phase 1 only) at the various time points.

1.2. Schema



Abbreviation: IRC = internal review committee.

Note: Participants ⩾16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

1.3. Schedule of Activities

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

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

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

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

All other participants (ie, those who were not eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations), at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests[b]	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s)[c]		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~50 mL + optional[e] ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration[d]		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←	—	→	←	→							
Review ongoing reactogenicity e-diary symptoms and obtain stop dates					X		X						
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	**Screening**	**Vax 1**	**Next-Day Follow-up Visit (Vax 1)**	**1-Week Follow-up Visit (Vax 1)**	**Vax 2**	**1-Week Follow-up Visit (Vax 2)**	**2-Week Follow-up Visit (Vax 2)**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**0 to 28 Days Before Visit 1**	**Day 1**	**1 to 3 Days After Visit 1**	**6 to 8 Days After Visit 1**	**19 to 23 Days After Visit 1**	**6 to 8 Days After Visit 4**	**12 to 16 Days After Visit 4**	**28 to 35 Days After Visit 4**	**175 to 189 Days After Visit 4**	**350 to 378 Days After Visit 4**	**714 to 742 Days After Visit 4**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
										ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2			
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)												X	X

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

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Administration of BNT162b2 to Those Originally Assigned to Placebo: If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study. When contacted, the site will conduct a phone visit to confirm eligibility and, if eligible and wanting to receive BNT162b2 if the participant originally received placebo, will unblind study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2, the participant will move to the SoA in Section 1.3.3 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

All other participants ≥16 years of age (ie, those who were not eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations) will be asked at Visit 4 if they wish to receive BNT162b2 if they originally received placebo prior to unblinding. If they want to receive BNT162b2, they will be unblinded and those who did originally receive placebo will move to the SoA in Section 1.3.3 for their remaining visits.

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

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

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

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

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

1.3.3. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. Any placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2.

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

Visit Number	101	102	103	104	105	Unplanned	Unplanned
Visit Description	**Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact**	**6-Month Telephone Contact**	**18-Month Telephone Contact**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**From Recommendation[a] or At Least 175 Days After Vaccination 2[b]**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**	**532 to 560 Days After Visit 102**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs and SAEs as appropriate	X	X	X	X		X[d]	X[d]
Contact the participant by telephone			X	X	X		
Request the participant return the e-diary or assist the participant to delete the application					X		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)						X	X

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

a. For participants who become eligible according to local/national recommendations (detailed separately, and available in the electronic study reference portal).
b. For all other Phase 2/3 placebo recipients who wish to receive BNT162b2; may be combined with Visit 4 for Phase 2/3 participants.
c. Only if the participant has no blood sample collected in the previous 7 days.
d. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

1.3.4. Surveillance for Asymptomatic SARS-CoV-2 Infection

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

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

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

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

2. INTRODUCTION

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

2.1. Study Rationale

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

2.2. Background

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

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

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[1] The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.[2] The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.[3]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[4,5]

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

traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.

- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

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

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials using modRNA influenza vaccines by Moderna,[7] the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

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

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available

therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

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

Updates as part of protocol amendment 7:

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

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

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

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

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

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2	
	• Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

3.2. For Phase 2/3

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

Objectives[a]	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	In participants complying with the key protocol criteria (evaluable participants) 1 month after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study

Objectives[a]	Estimands	Endpoints
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See Section 6.1.1 for description of the manufacturing process.

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

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

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

4. STUDY DESIGN

4.1. Overall Design

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

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

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

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

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

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

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

4.1.1. Phase 1

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

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

- Additional safety assessments (see Section 8.2)
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day

  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions

  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination

- Application of stopping rules

- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:

  - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)

  - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

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

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

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

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

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4.

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

4.1.2. Phase 2/3

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

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

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

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

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups

(12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

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

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

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

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

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

4.3. Justification for Dose

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

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

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

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

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and

- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20-µg dose level is formally included for both candidates.

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

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

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3), at randomization. Note that participants <18 years of age cannot be enrolled in the EU.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

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

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

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

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

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).Receipt of medications intended to prevent COVID-19.

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

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

   - Hypertension

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

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

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

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

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

10. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

11. Previous vaccination with any coronavirus vaccine.

12. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in

Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

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

Prior/Concurrent Clinical Study Experience:

15. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

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

Diagnostic Assessments:

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

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

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

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

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

Other Exclusions:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.4. Screen Failures

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

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

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

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

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:

    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;

- Sore throat;
- Diarrhea;
- Vomiting.

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

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

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

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

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

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

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

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

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

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

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. Participants ≥16 years of age who originally received placebo and accept the offer to receive BNT162b2 at defined points as part of the study will

receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the study's additional SoA (Section 1.3.3). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

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

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

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

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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

6.3.2. Blinding of Site Personnel

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

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

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

6.3.3. Blinding of the Sponsor

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

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

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

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

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

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

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

- When a participant who originally received placebo receives BNT162b2 per the SoA in Section 1.3.3, the study team will become unblinded to the participant's original study intervention allocation.

6.3.4. Breaking the Blind

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

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

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients will be provided separately: this unblinding will NOT be performed in the IRT.

6.4. Study Intervention Compliance

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

time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

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

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

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

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

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

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

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

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

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

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a

medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

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

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

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

6.6. Dose Modification

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

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of

BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see Section 8.15).

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;

- Participant request;
- Investigator request;
- Protocol deviation.

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

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

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic

period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

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

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

- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;

- Admission to an ICU;
- Death.

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

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

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

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

- SARS-CoV-2 neutralization assay
- Full-length S-binding or S1-binding IgG level assay
- RBD-binding IgG level assay (Phase 1 only)
- N-binding antibody assay

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

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

8.1.1. Biological Samples

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

development of other products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.1.2. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in Section 1.3.4.

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

8.2. Safety Assessments

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

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

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

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

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2. For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with Section 8.3.2.

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

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

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

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

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

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

8.2.2. Electronic Diary

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

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

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

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

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

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]

8.2.2.2. Local Reactions

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

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

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

Table 1. Local Reaction Grading Scale

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

8.2.2.3. Systemic Events

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

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

Table 2. Systemic Event Grading Scale

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

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

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

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

Table 3. Scale for Fever

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

8.2.2.5. Antipyretic Medication

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

8.2.3. Phase 1 Stopping Rules

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

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

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

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

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

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

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

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

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

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

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

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

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

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

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

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

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

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert

criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in Section 10.7.

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

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

8.2.6. Pregnancy Testing

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

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study

intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

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

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

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

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

OR

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

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

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

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

8.11. Study Procedures

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

8.11.1. Phase 1

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

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

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

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

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

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

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

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

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

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

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

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

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

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

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

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

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

- Record AEs as described in Section 8.3.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

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

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

- Record AEs as described in Section 8.3.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.

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

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

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

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

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

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).

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

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

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

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

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in Section 8.3.

- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in Section 10.2.

- Record nonstudy vaccinations as described in Section 6.5.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 10.4.

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

- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with Appendix 2.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.10. Between Visits 8 and 9

All participants who have not already been unblinded, at the approximate time participants in Phase 2/3 reach Visit 4, will be advised to contact the site to determine whether they can receive BNT162b2 as part of the study. When contacted, the site will unblind study intervention allocation to determine whether the participant received BNT162b1, BNT162b2, or placebo. If he or she originally received placebo and wants to receive BNT162b2, he or she will move to the procedures in Section 8.16.

8.11.1.11. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.1.12. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4): Only for Those Participants Who Originally Received BNT162b1 or BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2. Phase 2/3

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

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.

- Explain the e-diary technologies available for this study (see Section 8.14), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
    - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.14 for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

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

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

- Record AEs as described in Section 8.3.
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

- If Visit 3 is being conducted under amendment 10 onward: If the participant is ≥16 years of age, and is eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), determine if he/she is willing to receive BNT162b2 as part of the study. If so, unblind the participant's study intervention assignment, and move placebo recipients to the procedures in Section 8.16.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.5.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- If not already unblinded, unblind the participant's study intervention assignment, and move placebo recipients willing to receive BNT162b2 to the procedures in Section 8.16.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)): Only for Those Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.

- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;

- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;

- Fever;

- New or increased cough;

- New or increased shortness of breath;

- Chills;

- New or increased muscle pain;

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including
        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
        - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
        - Significant acute renal, hepatic, or neurologic dysfunction

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis
  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
  - Full blood count
  - Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
  - Number and type of any healthcare contact; duration of hospitalization and ICU stay
  - Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

- Asymptomatic SARS-CoV-2 infection surveillance visits: To determine the incidence of asymptomatic SARS-CoV-2 infection.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, asymptomatic SARS-CoV-2 infection surveillance visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

If a participant ≥16 years of age becomes eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal), the participant will be advised to contact the site to determine whether he or she can receive BNT162b2 as part of the study.

Placebo recipients ≥16 years of age who have not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Dose 2, and will follow the procedures listed in this section for the remainder of their participation in the study. For Phase 2/3 participants, Visit 101 could occur at the same time as the original Visit 4.

8.16.1. Visit 101 – Vaccination 3: (From Recommendation or at Least 175 Days After Vaccination 2)

Before vaccination and before any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign

the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

- Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.
- If the participant is receiving BNT162b2 following local/national recommendations, ensure he or she meets the recommending criteria (detailed separately, and available in the electronic study reference portal) OR ensure the participant is at least 175 days from Vaccination 2 (Visit 4/Visit 2, depending on the phase of the study).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.
- Discuss contraceptive use as described in Section 10.4.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.2. Visit 102 – Vaccination 4: (19 to 23 Days After Visit 101)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Record AEs as described in Section 8.3.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.6.

- Discuss contraceptive use as described in Section 10.4.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.

- Ensure and document that inclusion criteria 2, 3, and 5 are met and exclusion criteria 1, 3, 8, 10, 11, 12, 13, 16, 17, and 22 are not met.

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

- Obtain a nasal (midturbinate) swab (collected by site staff).

- Obtain the participant's vaccine vial allocation using the IRT system.

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

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4): (28 to 35 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.4. Visit 104 – 6-Month Follow-up Telephone Contact (After Vaccination 4): (175 to 189 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 103 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.16.5. Visit 105 – 18-Month Follow-up Telephone Contact (After Vaccination 4): (532 to 560 Days After Visit 102)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 104 (if any).
- Request the return of the participant's e-diary or assist the participant/participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant/participant's parent(s)/legal guardian that his or her study participation has ended.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17. Surveillance for Asymptomatic SARS-CoV-2 Infection

An intensive period of surveillance for asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11 until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner. The surveillance will be conducted per the procedures listed below.

Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

8.17.1. Visit 201– Asymptomatic SARS-CoV-2 Infection Surveillance Consent: From Approval of Protocol Amendment 11

Before surveillance begins and any study-related procedures are performed, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant/participant's parent(s)/legal guardian.

The visit should be conducted only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1) and this visit should be temporarily delayed until the symptoms have resolved.

- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3 for Phase 2/3 participants), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Record AEs as described in Section 8.3 (only if the participant remains in the AE reporting period; see Section 8.3.1).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 8.13.

- Ask the participant to obtain a surveillance self-swab at home in approximately 14 days or schedule an appointment for the participant to return to collect the swab at the site. The swab should be collected only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, a potential COVID-19 illness visit should be performed (see Section 8.13.1).

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17.2. Visit 202 Onward – Asymptomatic SARS-CoV-2 Infection Surveillance Swab: Repeating Every 10 to 18 Days After Each Previous Surveillance Swab Collection

This is a repeating swab collection and will be conducted approximately every 14 days until the intensive surveillance period ends.

- Participant collects a self-swab and ships it to the site for assessment at the central laboratory. The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). The swab should be collected as part of this visit only if the participant has no symptoms of potential COVID-19 (see Section 8.13). If the participant has such symptoms, the swab should be collected as part of a potential COVID-19 illness visit (see Section 8.13.1).

- Complete the source documents with the swab information.

- The investigator or an authorized designee completes the CRFs with the swab information.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in Section 3.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated

based on the lower bound of the 95% CI. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE >20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of

N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and

Population	Description
	determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.5.1. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Secondary immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level**

Endpoint	Statistical Analysis Methods
	For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. **Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for each investigational product within each group at each of the following time points:

Endpoint	Statistical Analysis Methods
	• Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 The Clopper-Pearson method will be used to calculate the CIs. **GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level** For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points: • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the 16- to 25-year age group)	**GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age** For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment.

Endpoint	Statistical Analysis Methods
	The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory immunogenicity	**Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3: • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level** For SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:

Endpoint	Statistical Analysis Methods
	• 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **RCDCs for immunogenicity results** Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG level after Dose 1 and after Dose 2.

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate

Endpoint	Statistical Analysis Methods
	in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.
Secondary	**First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group**

Endpoint	Statistical Analysis Methods
	Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group **Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints for COVID-19 illness according to CDC-defined symptoms will be evaluated descriptively with 95% CIs. **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** **Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group** VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Missing efficacy data will not be imputed.

Endpoint	Statistical Analysis Methods
	The following secondary efficacy endpoints regarding asymptomatic SARS-CoV-2 infection will be evaluated based on a success criterion of the lower bound of the 2-sided 95% CI for VE being >20%. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose for the active vaccine group to the placebo group** An asymptomatic case is defined as positive N-binding antibody at a post–Dose 2 visit (eg, Visit 3, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by negative N-binding antibody at Visit 1 and negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness. A secondary definition will be applied without the requirement for a negative NAAT at Visit 2. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without evidence of infection (up to the start of asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population and will include only participants who are consented to participate in the asymptomatic surveillance and who do not have serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

Endpoint	Statistical Analysis Methods
Exploratory	**Ratios of confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without, and with and without, evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group** After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4. Descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.[9] Supportive analysis of time to confirmed COVID-19 illness will be performed using the Cox proportional hazard model. Kaplan-Meier cumulative incidence curves will be provided. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. **Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted. **Ratio of asymptomatic SARS-CoV-2 infection through the blinded follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the

Endpoint	Statistical Analysis Methods
	corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. **Incidence of asymptomatic SARS-CoV-2 infection through the entire study follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study** Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2 at initial randomization and subsequently have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study. **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. Participants who are consented to participate in the asymptomatic surveillance and who have serological or virologic evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period will be included in the analysis.

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

Endpoint	Statistical Analysis Methods
	For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method[10] will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group. AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4.

Endpoint	Statistical Analysis Methods
	The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GFMR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” and each lot of “Process 2” will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing “Process 1” will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed

various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be

evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.

- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.

- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of “Process 1” and “Process 2” material, 1 month after Dose 2.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
    - Allow groups of participants of 65 to 85 years of age to proceed
    - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
    - Whether any groups may not be started
    - Whether any groups may be terminated early
    - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Up until the final efficacy analysis, 3 blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of "significant acute renal, hepatic, or neurologic dysfunction," the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial. When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form
• Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex

Abbreviation	Term
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

Abbreviation	Term
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see Section 9.6). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

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

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

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Protocol C4591001

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

Statistical Analysis Plan (SAP)

Version: 1

Date: 20 May 2020

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 20 May 2020	Protocol amendment 1 13 May 2020	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and tertiary/exploratory objective are described in Table 2 below.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis. However, this calculation may be adjusted based upon additional data from the assay.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing laboratory results to confirm COVID-19 infection will not be imputed for the primary analysis, but imputation of missing data for the efficacy endpoint may be performed as a sensitivity analysis.

Table 2. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints

Primary Objective	Estimands	Primary Endpoints
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses.	In participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, the percentage of participants reporting: • Local reactions for up to 7 days following each dose. • Systemic events for up to 7 days following each dose. • AEs from Dose 1 to 1 month after the last dose. • SAEs from Dose 1 to 6 months after the last dose. In addition, in sentinel cohorts from Stage 1, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2. • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2.	• Local reactions (pain at the injection site, redness, and swelling). • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). • AEs • SAEs Hematology and chemistry laboratory parameters detailed in the protocol, Section 10.2.
Secondary Objectives	**Estimands**	**Secondary Endpoints**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses.	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: ***Stage 1 Sentinel Cohorts***: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2. ***Stage 1 Nonsentinel Cohorts and Stage 2 Cohorts***: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2.	

Table 2. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints

	Stage 3 Cohort(s): 1, 12, and 24 months after Dose 2. • GMTs at each time point. • GMFR from before vaccination to each subsequent time point after vaccination. • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination.	SARS-CoV-2 serum neutralizing titers.
	• GMCs at each time point. • GMFR from before vaccination to each subsequent time point after vaccination. • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination.	SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels.
	• GMR, estimated by the ratio of the GM of SARS-CoV-2 serum neutralizing titers to the GM of SARS-CoV-2–specific binding antibody levels at each time point.	SARS-CoV-2 serum neutralizing titers. SARS-CoV-2-S1–specific binding antibody levels. SARS-CoV-2 RBD-specific binding antibody levels.
To evaluate the efficacy of prophylactic BNT162 vaccines against confirmed COVID-19.	In participants complying with the key protocol criteria (evaluable participants) following receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo].	COVID-19 incidence per 1000 person-years of follow-up.
Tertiary/Exploratory Objectives	**Estimands**	**Tertiary/Exploratory Endpoints**
To describe the relationship between SARS-CoV-2 serological parameters and: • NAAT-confirmed COVID-19. • Symptomatic SARS-CoV-2 infection. • Asymptomatic SARS-CoV-2 infection.		Nonvaccine-antigen SARS-CoV-2 antibody levels.

2.2. Study Design

2.2.1. Overall Design

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

The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:

- As a 2-dose (separated by 21 or 60 days) or single-dose schedule.
- At up to 3 different dose levels.
- In 3 age groups (18 through 55 years of age, 65 through 85 years of age, and 18 through 85 years of age [stratified as ≤55 or >55 years of age])

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

The study consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final-candidate/dose large-scale stage. These stages, and the progression between them, are detailed in the schema (protocol, Section 1.2).

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

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2.

2.2.2. Stage 1

Each group (vaccine candidate/dose level/age group/number of doses) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo. On Day 22, those in 2-dose groups will receive the same vaccine they received on Day 1; for those in single-dose groups, all will receive placebo. Full details of all potential groups in Stage 1 may be found in Table 3.

Table 3. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
2-Dose Groups (Sentinel Cohorts)			**Day 1**			**Day 22**		
a-0.1-2-Y (Sentinel) [uRNA 0.1 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)
a-0.3-2-Y (Sentinel) [uRNA 0.3 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)
a-1-2-Y (Sentinel) [uRNA 1 µg (2 doses)]	15	18 to 55	BNT162a1 Placebo	1 µg	(n=12) (n=3)	BNT162a1 Placebo	1 µg	(n=12) (n=3)
b1-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-Y (Sentinel) [modRNA 10 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-Y (Sentinel) [modRNA 30 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-Y (Sentinel) [modRNA 100 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
c-0.1-2-Y (Sentinel) [saRNA 0.1 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)
c-0.3-2-Y (Sentinel) [saRNA 0.3 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)
c-1-2-Y (Sentinel) [saRNA 1 µg (2 doses)]	15	18 to 55	BNT162c2 Placebo	1 µg	(n=12) (n=3)	BNT162c2 Placebo	1 µg	(n=12) (n=3)
a-0.1-2-O (Sentinel) [uRNA 0.1 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)	BNT162a1 Placebo	0.1 µg	(n=12) (n=3)
a-0.3-2-O (Sentinel) [uRNA 0.3 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)	BNT162a1 Placebo	0.3 µg	(n=12) (n=3)
a-1-2-O (Sentinel) [uRNA 1 µg (2 doses)]	15	65 to 85	BNT162a1 Placebo	1 µg	(n=12) (n=3)	BNT162a1 Placebo	1 µg	(n=12) (n=3)
b1-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	10 µg	(n=12) (n=3)	BNT162b1 Placebo	10 µg	(n=12) (n=3)
b1-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	30 µg	(n=12) (n=3)	BNT162b1 Placebo	30 µg	(n=12) (n=3)
b1-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)
b2-10-2-O (Sentinel) [modRNA 10 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	10 µg	(n=12) (n=3)	BNT162b2 Placebo	10 µg	(n=12) (n=3)
b2-30-2-O (Sentinel) [modRNA 30 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	30 µg	(n=12) (n=3)	BNT162b2 Placebo	30 µg	(n=12) (n=3)
b2-100-2-O (Sentinel) [modRNA 100 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	100 µg	(n=12) (n=3)	BNT162b2 Placebo	100 µg	(n=12) (n=3)
c-0.1-2-O (Sentinel) [saRNA 0.1 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)	BNT162c2 Placebo	0.1 µg	(n=12) (n=3)
c-0.3-2-O (Sentinel) [saRNA 0.3 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)	BNT162c2 Placebo	0.3 µg	(n=12) (n=3)

Table 3. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
c-1-2-O (Sentinel) [saRNA 1 µg (2 doses)]	15	65 to 85	BNT162c2 Placebo	1 µg	(n=12) (n=3)	BNT162c2 Placebo	1 µg	(n=12) (n=3)
Single-Dose Groups			**Day 1**			**Day 22**		
a-x-1-Y [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-Y [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-Y [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
a-x-1-O [uRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b1-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
b2-x-1-O [modRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162b2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
c-x-1-O [saRNA dose level(s) selected for Stage 2 (1 dose)]	15	65 to 85	BNT162c2 Placebo	TBD	(n=12) (n=3)	Placebo		(n=15)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
a-x-2L-Y [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-Y [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162b2 Placebo	TBD	(n=12) (n=3)	BNT162b2 Placebo	TBD	(n=12) (n=3)
c-x-2L-Y [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	18 to 55	BNT162c2 Placebo	TBD	(n=12) (n=3)	BNT162c2 Placebo	TBD	(n=12) (n=3)
a-x-2L-O [uRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162a1 Placebo	TBD	(n=12) (n=3)	BNT162a1 Placebo	TBD	(n=12) (n=3)
b1-x-2L-O [modRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162b1 Placebo	TBD	(n=12) (n=3)	BNT162b1 Placebo	TBD	(n=12) (n=3)
b2-x-2L-O	15	65 to 85	BNT162b2	TBD	(n=12)	BNT162b2	TBD	(n=12)

Table 3. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1	Dose 2
[modRNA dose level(s) selected for Stage 2 (2 doses)]			Placebo (n=3)	Placebo (n=3)
c-x-2L-O [saRNA dose level(s) selected for Stage 2 (2 doses)]	15	65 to 85	BNT162c2 TBD (n=12) Placebo (n=3)	BNT162c2 TBD (n=12) Placebo (n=3)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; saRNA = self-amplifying messenger ribonucleic acid; TBD = to be determined; uRNA = unmodified messenger ribonucleic acid.

For each vaccine candidate/dose level/age group, the 15 participants randomized into each 2-dose group will comprise a sentinel cohort, to which the following apply:

- Additional safety assessments (see protocol, Section 8.2)
- Controlled enrollment:
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day.
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions.
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
- Application of stopping rules.
- IRC review of safety data to determine escalation to the next dose level.
  - Escalation between dose levels in the 18- through 55-year age cohort will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01).
  - Escalation between dose levels in the 65- through 85-year age cohort will be based on IRC review of:
    - At least 4-week post–Dose 1 safety data for the corresponding dose level in the 18- through 55-year age cohort in this study and/or the BioNTech study conducted in Germany (BNT162-01) and,
    - At least 24-hour post–Dose 1 safety data in this study for the prior dose level in the 65- through 85-year age cohort.

- Note that, for candidates based upon the same RNA platform (eg, BNT162b1 and BNT162b2), the stated observation periods may be shortened to 24 hours for the second candidate studied, if the safety profile of the first candidate studied was deemed acceptable at the same dose level by the IRC.

Groups of participants 65 through 85 years of age will not be started until safety and immunogenicity data for the same RNA platform/dose level have been deemed acceptable in the 18- through 55-year age cohort by the IRC.

Once the IRC has selected a vaccine candidate/dose level to proceed into Stage 2, for each age cohort, 2 additional groups will be enrolled into Stage 1 for that vaccine candidate/dose level:

- A 2-dose group, with the 2 doses administered 60 days apart rather than 21 days.
- A 1-dose group.

In this stage, assuming 2 dose levels are selected following the initial dose escalation, up to 56 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 840 participants.

2.2.3. Stage 2

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 or more groups (vaccine candidate/dose level) may be selected to proceed into Stage 2. Participants in this stage will be 18 through 85 years of age, stratified equally: 18 through 55 or 56 through 85 years. Commencement of each age stratum will be dependent upon satisfactory safety and immunogenicity data from the 18- through 55-year and 65- through 85-year groups from Stage 1, respectively. It is therefore possible that the 2 age strata may not start concurrently.

In each group selected for Stage 2, it is intended that 225 participants will be randomized in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

2.2.4. Stage 3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 group may be selected to proceed into Stage 3. Participants in this stage will be 18 through 85 years of age, stratified equally: 18 through 55 years or 56 through 85 years. As in Stage 2, it is possible that the 2 age strata may not start concurrently.

The group receiving the vaccine candidate/dose level selected for Stage 3 will comprise 3000 participants. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

For participants receiving at least 1 dose of study intervention and having safety data reported after any vaccination, below are the primary safety endpoints:

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each dose in each vaccine group.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose in each vaccine group.

For participants receiving at least 1 dose of study intervention, below are the primary safety endpoints:

- AEs from Dose 1 to 1 month after the last dose.
- SAEs from Dose 1 to 6 months after the last dose.

For participants in sentinel cohorts from Stage 1, below are the additional primary safety endpoints:

- Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2.

3.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 for each dose, where Day 1 is the day of each dose, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7);
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

For each local reaction and any local reaction on any day, Table 4 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of each dose.

Table 4. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.

Table 4. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for each and any of the local reactions (redness, swelling, and pain at the injection site) and for each and any of the severe local reactions within the interval from Day 1 through Day 7 after each dose.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 5.

Table 5. Local Reaction Grading Scale

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

For each local reaction reported for each dose, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each dose) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 5), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. However, if an event is ongoing to the time of a subsequent vaccination, the end date/day for the ongoing event would be the date/day that the next vaccine is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if participants report change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are vomiting, diarrhea, headache, fatigue/tiredness, chills, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the way local reactions are handled for presence of event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.1). Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 7 for summary of maximum temperature.

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

Oral temperature will be collected in the evening, daily, for 7 days following each dose (Days 1 through 7, where Day 1 is the day of each dose) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 7. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius first for reporting. Fever will be grouped into ranges for the analysis according to Table 7 below.

Table 7. Scale for Fever

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

Note: Fever is defined as temperature ≥38.0°C (≥100.4°F).

3.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7);
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7);
- Duration (first to last day reported) of use of antipyretic medication;
- Onset day of use of antipyretic medication.

  The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after the last dose.

The primary endpoint "AEs from Dose 1 through 1 month after the last dose" and other AE endpoints will be summarized by SOC and PT at the participant level.

This primary endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose).

AE reporting will be based on the specific reporting period. Standard algorithms for handling missing AE dates will be applied as described in the Pfizer Vaccine data standard rules.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's Safety Review Plan.
- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 1% participants with the AE term in at least 1 vaccine group.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

3.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Stage 1 sentinel-cohort participants, Visit 5 for Stage 1 nonsentinel-cohort participants and Stage 2 participants, and Visit 4 for Stage 3 participants).

The safety endpoint "SAEs from Dose 1 to 6 months after the last dose" will be summarized by SOC and PT at the participant level.

3.1.6. Hematology and Chemistry Laboratory Parameters in Sentinel Cohorts From Stage 1

The following safety laboratory tests will be performed at the times defined in the protocol, Section 1.3 (schedule of activities). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry
Hemoglobin	BUN and creatinine
Hematocrit	AST, ALT
RBC count	Total bilirubin
MCV	Alkaline phosphatase
MCH	
MCHC	
Platelet count	
WBC count	
Total neutrophils (Abs)	
Eosinophils (Abs)	
Monocytes (Abs)	
Basophils (Abs)	
Lymphocytes (Abs)	

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 8). Additionally, the primary criterion for abnormality will follow the Pfizer safety rule book.

Table 8. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0

Table 8. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm^3	2500 – 3500	1500 – 2499	1000 – 1499	<1000
Lymphocytes decrease - cells/mm^3	750 – 1000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1500 – 2000	1000 – 1499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Alkaline phosphate - increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	>10 × ULN
Liver function tests - ALT, AST increase by factor	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10 × ULN
Bilirubin - when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	>1.75 × ULN
Bilirubin - when liver function test is normal - increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	>3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

- SARS-CoV-2 serum neutralizing titers.
- SARS-CoV-2-S1–specific binding antibody levels.
- SARS-CoV-2 RBD-specific binding antibody levels.

To support the secondary immunogenicity endpoints, the GMTs or concentrations at all time points, GMFR from before vaccination to each subsequent time point after vaccination, and proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination will be calculated and summarized by vaccine group.

3.2.1.1. Serum Neutralizing Titers

Titers above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

3.2.1.2. IgG Concentrations

Results will be reported as IgG concentrations. IgG concentrations above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

3.2.2. Vaccine Efficacy Endpoint

- COVID-19 incidence per 1000 person-years of follow-up 14 days after receipt of the last dose of study intervention onwards.

3.3. Tertiary/Exploratory Endpoints

- Nonvaccine-antigen SARS-CoV-2 antibody levels.

3.4. Baseline and Other Variables

Measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments.

The following variables will be summarized as part of the baseline characteristics:

- Demographics
- Medical history
- Physical examination

- Vital signs

Other variables to be summarized include the following:

- E-diary completion
- Prior/concomitant vaccines
- Concomitant medications

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at Dose 1 (in years), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the time of vaccination (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 19th birthday, the participant is considered to be 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at Dose 1 for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA.

A physical examination will be performed. It will evaluate any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Clinically significant abnormal results will be recorded in the CRF.

3.4.2. E-Diary Completion

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Stage 1 sentinel cohorts, Visit 5 for Stage 1 nonsentinel cohorts and Stage 2 participants, and Visit 4 for Stage 3 participants).

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

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

Concomitant and prior vaccines, and concomitant medications will be coded using the WHO Drug Dictionary.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the primary safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per SOPs.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result 21 days after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other major protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other major protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive vaccination(s) as randomized within the predefined window, have the efficacy measurement after the last dose of study intervention, and have no other major protocol deviations as determined by the clinician.
All-available efficacy	All eligible randomized participants who receive at least 1 vaccination and have the efficacy measurement at any time after Dose 1.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

The major protocol deviations will be determined by the medical monitor. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity/efficacy, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with major protocol deviations before any unblinded analysis in Stage 3 is carried out.

Both evaluable and all-available populations will be used for immunogenicity analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded. Sponsor staff will be unblinded to vaccine allocation for the participants in Stage 1 and Stage 2. Laboratory personnel performing the assays will remain blinded until all assays are completed. The timing for statistical analyses is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Vaccine Efficacy Hypothesis

At the end of Stage 3, the VE will be evaluated. VE is defined as VE = 100 × (1 – IRR), where IRR is the calculated ratio of the COVID-19 illness rate in the active vaccine group to the illness rate in the placebo group. The efficacy hypothesis is:

H_0: VE ≤20% vs H_a: VE >20%

where H_0 and H_a represent the null hypothesis and alternative hypothesis. For participants with multiple illnesses, only the first COVID-19 confirmed case will contribute to the VE calculation in the hypothesis test.

The main efficacy endpoint will be confirmed by SARS-CoV-2 NAAT-positive results at a central laboratory, ie, centrally confirmed COVID-19, with the presence of at least 1 symptom described in the protocol, Section 8.13.

Efficacy will be demonstrated if the null hypothesis VE ≤20% is rejected at the 0.025 significance level, that is, when the lower limit of the 2-sided 95% CI for VE is >20%, which is derived using the Clopper-Pearson method as described by Agresti.[1]

5.1.2. Sample Size

The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. Stage 1 will comprise 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; up to 56 potential groups are foreseen; if all groups are fully enrolled, assuming 2 dose levels are selected following the initial dose escalation, this corresponds to a total of 840 participants. Stage 2 will include 1 or more vaccine groups selected from Stage 1, and 225 participants will be randomized per selected vaccine candidate in a 4:1 ratio to receive active vaccine (180 participants) or placebo (45 participants).

For Stage 3, for the selected vaccine candidate/dose level, with assumptions of a true VE of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants per group (1:1 randomization ratio), based on the assumption of a 1.7% incidence rate in the placebo group, and 20% of the participants being nonevaluable.

For safety outcomes, Table 9 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 9. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000
0.10%	0.01	0.04	0.16	0.95
0.50%	0.06	0.20	0.59	>0.99
1.00%	0.11	0.36	0.84	>0.99
2.00%	0.22	0.60	0.97	>0.99
3.00%	0.31	0.75	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99

5.1.3. Multiplicity Considerations

Since there is only 1 hypothesis with regard to VE at Stage 3, and no interim analysis is planned for efficacy evaluation, no multiplicity adjustment is required to control the type I error rate.

5.2. General Methods

Time points for local reactions and systemic events refer to data within 7 days after each dose.

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen[2] method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

5.2.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Means

For immunogenicity results of SARS-CoV-2 serum neutralizing titers, the GMTs will be computed along with associated 95% CIs. The GM will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of concentrations, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. Similarly, GMCs and 95% CIs will be calculated for SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels.

5.2.2.2. Geometric Mean Fold Rises

GMFRs will be defined as the result after vaccination divided by the result before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed neutralization titers or antibody levels (later result minus earlier result) and exponentiating the mean. The associated 2-sided 95% CIs are obtained by constructing CIs using Student's t-distribution for the mean difference on the natural log scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels, the GMRs will be provided along with associated 95% CIs.

GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody/SARS-CoV-2 RBD-specific binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2-S1–specific binding antibody for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.4. Geometric Mean Fold Rise Ratios

The ratios of GMFR A to GMFR B and GMFR A to GMFR C may be explored, where GMFR A is the GM of the ratio of the SARS-CoV-2 serum neutralizing titer at the time point after vaccination to the corresponding titer at the time point before vaccination, GMFR B is the GM of the ratio of the SARS-CoV-2-S1–specific binding antibody level at the time point after vaccination to the corresponding antibody level at the time point before vaccination, and GMFR C is the GM of the ratio of the SARS-CoV-2 RBD-specific binding antibody level at the time point after vaccination to the corresponding antibody level at the time point before vaccination.

5.2.2.5. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

5.3. Methods to Manage Missing Data

For endpoints, the missing data handling rules are described in the corresponding endpoint sections.

For the missing dates, the sponsor data standard rules for imputation will be applied (eg, partial dates for AEs will be imputed according to Pfizer standard algorithms).

Missing COVID-19 test data in Stage 3 for computing VE will be imputed in the sensitivity analysis. Details are included in Section 6.2.2.1.3.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

6.1.1. Local Reactions

6.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each and any local reaction after each dose in each vaccine group will be presented by maximum severity across severity levels. Confirmed e-diary errors will be excluded from the analysis. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2. Supplementary Analyses

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1) will be summarized with the same analysis time point and analysis population, analysis methodology, and appropriate reporting results. Confirmed e-diary errors will be excluded from these analyses.

- Duration (days) of each local reaction after each dose.
- Onset day of each local reaction after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days will be plotted for each vaccine group. The bars will be divided into severity to highlight the proportions of participants by maximum severity.

6.1.2. Systemic Events

6.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group will be presented by maximum severity across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.2.2. Supplementary Analyses

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after each dose.
- Onset day of each systemic event after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

The use of antipyretic medication (see Section 3.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days after each dose will be plotted for each vaccine group. The bars will be divided into severity subgroups to highlight the proportions of participants by severity.

6.1.3. Adverse Events

6.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 to 1 month after the last dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 1 month after the last dose.
- Analysis methodology: 3-Tiered approach (Section 3.1.4).
- Intercurrent events and missing data: Partial AE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: AEs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers (Section 3.1.4). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[2] method will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within SOC. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs for each vaccine group.

6.1.3.2. Supplementary Analyses

Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.4. Serious Adverse Events

6.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 1 to 6 months after the last dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 6 months after the last dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Partial SAE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group.

6.1.5. Hematology and Chemistry Parameters in Sentinel Cohorts From Stage 1

6.1.5.1. Main Analyses

- Estimands: The percentage of participants with abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 (Section 2.1).
- The percentage of participants with grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Analysis methodology: Descriptive statistics including counts and percentage (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive summary statistics will be provided including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

For all immunogenicity analyses, the same analysis methods will be applied to the immunogenicity endpoints in Stages 1, 2, and 3. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations (Section 4). Participants will be summarized according to the vaccine group to which they were randomized. The missing serology data will not be imputed. The summary for additional immunogenicity assay results will be provided, if any.

6.2.1.1. SARS-CoV-2 Serum Neutralizing Titers

6.2.1.1.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).
  - Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination (Section 2.1).
- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points:
  - Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.
  - Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2.
  - Stage 3 cohort(s): 1, 12, and 24 months after Dose 2.
- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results Section 5.2.2.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming

the limits back to the original scale (Section 5.2.2.2). Percentages of participants with ≥4-fold rise will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.

- Reporting results: the GMTs at each time point, GMFRs from before vaccination to each subsequent time point after vaccination, and the percentages of participants achieving ≥4-fold rise and the associated 2-sided 95% CIs from before vaccination to each time point after vaccination.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 serum neutralizing titers after Dose 1 and after Dose 2 (Section 5.2.2.5).

6.2.1.1.2. Additional Exploratory Analyses

Similar analysis for SARS-CoV-2 serum neutralizing titers will be performed by baseline serostatus (< LLOQ and ≥ LLOQ).

6.2.1.2. SARS-CoV-2-S1–Specific Binding Antibody Levels and RBD-Specific Binding Antibody Levels

6.2.1.2.1. Main Analyses

- Estimands:
    - GMCs (Section 2.1).
    - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).
    - Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination (Section 2.1).
- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points:
    - Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.

  - Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2.

  - Stage 3 cohort(s): 1, 12, and 24 months after Dose 2.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results (Section 5.2.2.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale (Section 5.2.2.2). Percentages of participants with ≥4-fold rise will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.

- Reporting results: the GMCs, GMFRs, and percentages of participants with ≥4-fold rise and the associated 2-sided 95% CIs will be provided for each study intervention (active/placebo) within each group before vaccination and at each time point.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels after Dose 1 and after Dose 2 (Section 5.2.2.5).

6.2.1.2.2. Additional Exploratory Analyses

Similar analysis for SARS-CoV-2-S1–specific binding antibody levels and RBD-specific binding antibody levels will be performed by baseline serostatus.

6.2.1.3. GMR of SARS-CoV-2 Serum Neutralizing Titer to SARS-CoV-2-S1–Specific Binding Antibody Levels and RBD-Specific Binding Antibody Levels

6.2.1.3.1. Main Analyses

- Estimands:
  - GMR of SARS-CoV-2 serum neutralizing titers to SARS-CoV-2-S1–specific binding antibody levels (Section 2.1).
  - GMR of SARS-CoV-2 serum neutralizing titers to SARS-CoV-2 RBD-specific binding antibody levels (Section 2.1).
- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points:
  - Stage 1 sentinel cohorts: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.
  - Stage 1 nonsentinel cohorts and Stage 2 cohorts: 21 days after Dose 1; 14 days and 1, 6, 12, and 24 months after Dose 2.
  - Stage 3 cohort(s): 1, 12, and 24 months after Dose 2.
- Analysis methodology: GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2-S1–specific binding antibody/SARS-CoV-2 RBD-specific binding antibody at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 serum neutralizing titers minus SARS-CoV-2-S1–specific binding antibody levels for each participant) and transformed back to the original scale (Section 5.2.2.3). Two-sided CIs will be obtained by calculating CIs using the Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale (Section 5.2.2.3).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: The GMRs and the associated 2-sided 95% CIs will be provided for each study intervention (active/placebo) within each group before vaccination and at each time point.

6.2.2. Vaccine Efficacy Endpoints

6.2.2.1. COVID-19 Incidence per 1000 Person-Years of Follow-up

6.2.2.1.1. Main Analyses

- Estimand: 100 × (1 – IRR) [ratio of active vaccine illness rate to placebo illness rate] (Section 2.1).

- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).

- Analysis time point: End of the surveillance period (ie, 53 COVID-19 cases were observed).

- Analysis methodology: Assessment of VE will be performed for centrally confirmed COVID-19 from 14 days after the receipt of the last dose of study intervention onwards, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of COVID-19 illness rate per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group after 2 doses. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method.

- Intercurrent events and missing data: COVID-19 test data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing efficacy data will not be imputed in the main analyses.

- Reporting results: VE and the associated 2-sided 95% CIs will be provided.

6.2.2.1.2. Additional Exploratory Analyses

The same methodology described in Section 6.2.2.1.1 for VE assessment will be applied to the following exploratory endpoints to evaluate:

- VE for centrally confirmed COVID-19 from 1 day after the receipt of the first dose of study intervention onwards.

- VE for centrally confirmed COVID-19 from 1 day after the receipt of the first dose and 14 days after the receipt of the last dose of study intervention onwards by baseline serostatus based on SARS-CoV-2-S1–specific binding antibody levels.

- VE for locally confirmed COVID-19 from 1 day after the receipt of the first dose and 14 days after the receipt of the last dose of study intervention onwards.

- VE for locally confirmed COVID-19 from 1 day after the receipt of the first dose and 14 days after the receipt of the last dose of study intervention onwards by baseline serostatus based on SARS-CoV-2-S1–specific binding antibody levels.

- VE for centrally confirmed symptomatic seroconversion to SARS-CoV-2 from 1 day after the receipt of the first dose and 14 days after the receipt of the last dose of study intervention onwards: presence of at least 1 symptom described in the protocol, Section 8.13, and a positive nonvaccine-antigen SARS-CoV-2 antibody result in a participant whose most recent prior nonvaccine-antigen SARS-CoV-2 antibody result was negative.

- VE for centrally confirmed asymptomatic seroconversion to SARS-CoV-2 from 1 day after the receipt of the first dose and 14 days after the receipt of the last dose of study intervention onwards: positive nonvaccine-antigen SARS-CoV-2 antibody result in a participant with a prior nonvaccine-antigen SARS-CoV-2 antibody result that was negative.

6.2.2.1.3. Sensitivity and Supplemental Analyses

With MAR assumption, a missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method.[3] The imputation will run multiple times (up to 1000) and summary statistics (eg, average VE, number and percentage of lower limit of 95% CI for VE >20%, etc, from the imputation runs) across the imputations will be tabulated.

COVID-19 disease-related information may be summarized or listed.

6.3. Tertiary/Exploratory Endpoints

6.3.1. Relationship Between SARS-CoV-2 Serological Parameters and NAAT-Confirmed COVID-19, Symptomatic SARS-CoV-2 Infection, and Asymptomatic SARS-CoV-2 Infection

If sufficient data are collected, the correlation of RT-PCR–confirmed COVID-19 and seropositivity or seroconversion measured by nonvaccine-antigen SARS-CoV-2 antibody levels, percentages (and 2-sided 95% CIs) of participants with confirmed COVID-19, and nonvaccine-antigen SARS-CoV-2 antibody levels after Dose 1 and after Dose 2 will be provided.

6.3.2. Additional Analysis

The ratios of GMFRs may be explored (Section 5.2.2.4).

6.4. Subgroup Analysis

Subgroup analyses based on race, ethnicity, and sex will be performed on all primary safety and secondary immunogenicity and efficacy endpoints (as supplemental analyses).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including sex, race, and ethnicity, will be summarized for the safety population for each vaccine group and overall.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a SOC and PT according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group and overall by cohort for the overall safety population.

6.5.1.3. Physical Examination

Significant physical examination findings will be recorded on medical history or AE CRF pages, as relevant, and reporting will be done under those endpoints for the overall safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (Doses 1 and 2), who completed the follow-up visits (1 month after the last dose), and who withdrew before each follow-up visit along with the reasons for withdrawal will be tabulated by vaccine group (according to randomized group assignment) and overall by each cohort. The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately along with the reasons for exclusion, by vaccine group.

6.5.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-specified time frames will be tabulated separately for each time point.

6.5.2.3. E-Diaries

The participants who were vaccinated and completed e-diaries after each dose will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1 and Section 6.1.2, the summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and completing the e-diary for any day in the required reporting period, by assigned vaccine group for each dose.

The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for all randomized participants. The denominator for the percentages is the total number of participants in the given vaccine group or overall.

In addition, the relation of randomized vaccine to actual vaccine received will be presented as a cross tabulation of the actual vaccine received versus the randomized vaccine.

A listing of participants showing the randomized vaccine and the vaccine actually received at each dose will be presented.

6.5.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification. All vaccines received before Dose 1 will be listed. The number and percentage of randomized participants receiving each concomitant vaccine after Dose 1 will be tabulated according to assigned vaccine schedule. Summarization will be done for the interval between Dose 1 and 1 month after the last dose. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analyses

Local reaction, systemic event, AE, and SAE summaries and analyses are described under Primary Endpoint(s) (Section 6.1).

7. ANALYSES TIMING

7.1. Introduction

No formal interim analysis is planned in this study. As this is a sponsor open-label study during Stages 1 and 2, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 1.
- Complete safety and immunogenicity analysis approximately 3 weeks after Dose 2 for Stage 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Stage 3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available at the end of the study.

7.2.1. Data Monitoring Committee

This study will use an IRC and a DMC. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the roles of the IRC and DMC in more detail.

8. REFERENCES

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2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

3. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16(3):219-42.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BLQ	below the level of quantitation
BUN	blood urea nitrogen
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IgG	immunoglobulin G
IRC	internal review committee
IRR	illness rate ratio
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NAAT	nucleic acid amplification test
PT	preferred term
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
SOP	standard operating procedure
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization

Protocol C4591001

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

Statistical Analysis Plan (SAP)

Version: 4

Date: 08 Jan 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
1/ 20 May 2020	Protocol amendment 1, 13 May 2020	N/A
2/ 30 Jul 2020	Protocol amendment 5, 24 July 2020	Implemented the changes made in protocol amendments 2 through 5.
3/ 02 Nov 2020	Protocol amendment 9, 29 Oct 2020	Implemented the changes made in protocol amendments 6 through 9.
4/ 08 Jan 2021	Protocol amendment 11, 04 Jan 2021	Implemented the changes made in protocol amendments 10 and 11.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and tertiary/exploratory objective are described in Table 2 and Table 3 below.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by the all-available efficacy populations. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

Table 2. List of Primary and Secondary Objectives, Estimands, and Endpoints for Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in the protocol, Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination • Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers S1-binding IgG levels and RBD-binding IgG levels

Table 2. List of Primary and Secondary Objectives, Estimands, and Endpoints for Phase 1

Objectives	Estimands	Endpoints
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

Table 3. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints for Phase 2/3

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

Table 3. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints for Phase 2/3

Objectives[a]	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

Table 3. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints for Phase 2/3

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

Table 3. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints for Phase 2/3

Objectives[a]	Estimands	Endpoints
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 through the blinded follow-up period in participants without evidence of infection or confirmed COVID-19 during the study	In participants complying with the key protocol criteria (evaluable participants) 6 months after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2	In participants who received BNT162b2 at initial randomization 6, 12, and 24 months after receipt of the second dose of study intervention: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above

Table 3. List of Primary, Secondary, and Tertiary/Exploratory Objectives, Estimands, and Endpoints for Phase 2/3

Objectives[a]	Estimands	Endpoints
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See the protocol, Section 6.1.1, for description of the manufacturing process.

2.2. Study Design

2.2.1. Overall Design

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

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

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

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

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

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

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

2.2.2. Phase 1

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

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

- Additional safety assessments (see protocol, Section 8.2).
- Controlled enrollment (required only for the first candidate and/or dose level studied):
    - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day.
    - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions.
    - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
- Application of stopping rules.
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
    - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01).
    - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC.

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

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

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

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

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity at the approximate time participants in Phase 2/3 reach Visit 4.

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

2.2.3. Phase 2/3

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

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

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

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after

Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

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

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations (detailed separately, and available in the electronic study reference portal) will have the opportunity to receive BNT162b2 as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity from 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

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

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

this objective, whichever is sooner, per the SoA in the protocol, Section 1.3.4. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who originally received placebo and become eligible for receipt of BNT162b2 according to local or national recommendations and then receive BNT162b2 as part of the study will not participate in surveillance for asymptomatic SARS-CoV-2 infection; if they become eligible during the surveillance period, the swabbing every 2 weeks will cease.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Endpoints

For all participants in Phase 1, and a subset of at least 6000 participants randomized in Phase 2/3, receiving at least 1 dose of study intervention, below are the primary safety endpoints for local reactions and systemic events:

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each dose in each vaccine group.
- Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose in each vaccine group.

For all participants randomized in Phase 1 and Phase 2/3, receiving at least 1 dose of study intervention, below are the primary safety endpoints for AEs and SAEs (the last dose in Phase 1 is the second dose):

- AEs from Dose 1 to 1 month after the second dose.
- SAEs from Dose 1 to 6 months after the second dose.

In addition, for the first 360 participants randomized in Phase 2/3 (Phase 2 portion), receiving at least 1 dose of study intervention, below are the primary safety endpoints for AEs and SAEs:

- AEs from Dose 1 to 7 days after the second dose.
- SAEs from Dose 1 to 7 days after the second dose.

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 for each dose, where Day 1 is the day of each dose, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7);
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

For each local reaction and any local reaction on any day, Table 4 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of each dose.

Table 4. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for each and any of the local reactions (redness, swelling, and pain at the injection site) and for each and any of the severe local reactions within the interval from Day 1 through Day 7 after each dose.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 5.

Table 5. Local Reaction Grading Scale

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

For each local reaction reported for each dose, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each dose) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 5), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. However, if a reaction is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing reaction would be the date/day that the next vaccine is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if participants report change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are vomiting, diarrhea, headache, fatigue/tiredness, chills, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the way local reactions are handled for presence of event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.1.1). Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 7 for summary of maximum temperature.

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

Oral temperature will be collected in the evening, daily, for 7 days following each dose (Days 1 through 7, where Day 1 is the day of each dose) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 7 below.

Table 7. Scale for Fever

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

Note: Fever is defined as temperature ≥38.0°C (≥100.4°F).

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7);
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7);
- Duration (first to last day reported) of use of antipyretic medication;
- Onset day of use of antipyretic medication.

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after the second dose.

The primary endpoint "AEs from Dose 1 to 1 month after the second dose" and other AE endpoints will be summarized by SOC and PT at the participant level.

This primary endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose).

AE reporting will be based on the specific reporting period. Standard algorithms for handling missing AE dates will be applied as described in the Pfizer Vaccine data standard rules.

For Phase 2/3 only, a 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's Safety Review Plan.
- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 1% participants with the AE term in at least 1 vaccine group.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

3.1.1.5. Serious Adverse Events

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

The safety endpoint "SAEs from Dose 1 to 6 months after the second dose" will be summarized by SOC and PT at the participant level.

3.1.1.6. Hematology and Chemistry Laboratory Parameters (for Phase 1 Only)

For participants in Phase 1, below are the additional primary safety endpoints:

- Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2.

The following safety laboratory tests will be performed at the times defined in the protocol, Section 1.3 (schedule of activities). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry
Hemoglobin	BUN and creatinine
Hematocrit	AST, ALT
RBC count	Total bilirubin
MCV	Alkaline phosphatase
MCH	
MCHC	
Platelet count	
WBC count	
Total neutrophils (Abs)	
Eosinophils (Abs)	
Monocytes (Abs)	
Basophils (Abs)	
Lymphocytes (Abs)	

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 8). Additionally, the primary criterion for abnormality will follow the Pfizer safety rule book.

Table 8. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm^3	2500 – 3500	1500 – 2499	1000 – 1499	<1000
Lymphocytes decrease - cells/mm^3	750 – 1000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1500 – 2000	1000 – 1499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Alkaline phosphate - increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	>10 × ULN
Liver function tests - ALT, AST increase by factor	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10 × ULN

Table 8. Laboratory Abnormality Grading Scale

Bilirubin - when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	>1.75 × ULN
Bilirubin - when liver function test is normal - increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	>3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

3.1.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (prior to 7 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 7 days after the second dose).

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT (counting cases from 7 days after the second dose).

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

Phase 1

In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention:

- 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.

Below are the secondary immunogenicity endpoints for Phase 1:

- SARS-CoV-2 neutralizing titers.

- S1-binding IgG levels.

- RBD-binding IgG levels.

Phase 2/3

In participants with no serological or virological evidence of past SARS-CoV-2 infection, 12 to 15 years of age and 16 to 25 years of age complying with the key protocol criteria (evaluable participants) 1 month after Dose 2, below is the secondary immunogenicity endpoint for Phase 2/3:

- SARS-CoV-2 neutralizing titers.

3.2.1.1. Neutralizing Titers

Titers above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

3.2.1.2. IgG Concentrations

Results will be reported as IgG concentrations. IgG concentrations above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

To support the secondary immunogenicity endpoints, the GMTs or concentrations at all time points, GMFR from before vaccination to each subsequent time point after vaccination, and proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination will be calculated and summarized by vaccine group.

3.2.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (prior to 14 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 14 days after the second dose).

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT (counting cases from 14 days after the second dose).

- Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (prior to 7 days and prior to 14 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 7 days and 14 days after the second dose).

- Confirmed severe COVID-19 incidence per 1000 person-years of follow-up (counting cases from 7 days and 14 days after the second dose).

- According to the CDC-defined symptoms, COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (prior to 7 days and prior to 14 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 7 days and 14 days after the second dose).

- According to the CDC-defined symptoms, COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT (counting cases from 7 days and 14 days after the second dose).

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose.

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection.

3.3. Exploratory Endpoints

3.3.1. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

- COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT in participants without, and with and without, evidence of infection (counting cases from 7 days after the second dose).

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants who received BNT162b2 at initial randomization or subsequently (counting cases from 7 days after the second BNT162b2 vaccination).

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of blinded follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study.

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study.

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection.

3.3.2. Immunogenicity Endpoints (for Phase 2/3 Only)

In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention:

- Baseline and 1, 6, 12, and 24 months after completion of vaccination.

Below are the exploratory immunogenicity endpoints for Phase 2/3:

- SARS-CoV-2 neutralizing titers.
- Full-length S-binding or S1-binding IgG levels.

3.3.3. Additional Endpoints (for Phase 2/3 Only)

- All safety, immunogenicity, and efficacy endpoints described above will be summarized separately for participants with confirmed stable HIV.
- AEs, SAEs, and SARS-CoV-2 neutralizing titers will be summarized separately for participants 16 to 55 of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2." All participants who received "Process 2" vaccine and a random sample of 250 participants 16 to 55 years of age selected from those who received "Process 1" vaccine will be included for the side-by-side descriptive summary of "Process 1" and each lot of "Process 2."

3.4. Baseline and Other Variables

Measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at Dose 1 (in years), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis. For Phase 2/3, BMI will also be included in the demographic variables.

Age at the time of vaccination (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 19th birthday, the participant is considered to be 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at Dose 1 for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA. Comorbidities that increase the risk for severe COVID-19 illness will be categorized based on medical history terms.

For Phase 1, a physical examination will be performed. It will evaluate any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Clinically significant abnormal results will be recorded in the CRF.

For Phase 2/3, If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, physical examination will be performed and recorded any findings in the source documents and, if clinically significant, it will be recorded on the medical history CRF.

3.4.2. E-Diary Completion

For all participants in Phase 1, and a subset of at least 6000 in Phase 2/3, an e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in the protocol, Section 6.5.1, will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the primary safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per SOPs.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.

Population	Description
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result from the blood collection within an appropriate window after Dose 1 (same as visit window, ie, within 19-23 days after Dose 1), and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood collection within an appropriate window after Dose 2 (within 6-8 days after Dose 2 for Phase 1 and within 28-42 days after Dose 2 for Phase 2/3), and have no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy (7 days)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
Evaluable efficacy (14 days)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 14 days after Dose 2.
Evaluable efficacy (1 month)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have N-binding antibody test result available at the 1-month post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician on or before 1 month after Dose 2.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), consented to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.

Population	Description
All-available efficacy	Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination. Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity/efficacy, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis in Phase 2/3 is carried out.

5. GENERAL METHODOLOGY AND CONVENTIONS

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 6.3. The timing for statistical analyses is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Vaccine Efficacy Hypothesis

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the active vaccine group to the corresponding illness rate in the placebo group (see Appendix 3 for details on the calculation of IRR and VE). The assessment of VE will be based on posterior probabilities of VE_1 >30% and VE_2 >30% using beta-binomial models. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (high posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a beta-binomial model (see Appendix 2 for details).

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic

SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI calculated using the Clopper-Pearson method. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

5.1.2. Immunogenicity Hypothesis

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2**.** If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

5.1.3. Sample Size

Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of study intervention, a total of approximately 164 first confirmed COVID-19 illness cases will provide approximately 90% power. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE>20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who

are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 9).

For safety outcomes, Table 10 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 9. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

Table 10. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	>0.99	>0.99	>0.99	>0.99

Table 10. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000	N=6000	N=9000	N=15000
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

5.1.4. Multiplicity Considerations

For Phase 1, there is no hypothesis testing. For Phase 2/3, a Bayesian approach will be applied for the first primary efficacy endpoint at the interim and final analyses. The boundaries for declaring efficacy at interim analyses and success criteria for the final analysis are adjusted appropriately to control the type I error at 0.025 (Table 13).

5.2. General Methods

Time points for local reactions and systemic events refer to data within 7 days after each dose. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n), and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

For Phase 2/3 only, the 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen[2] method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

A Bayesian beta-binomial model with a minimally informative prior will be also used for VE primary endpoints (see Appendix 2).

5.2.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Means

For immunogenicity results of SARS-CoV-2 neutralizing titers, the GMTs will be computed along with associated 95% CIs. The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of titers, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits. Similarly, GMCs and 95% CIs will be calculated for S1-binding IgG levels and RBD-binding IgG levels.

5.2.2.2. Geometric Mean Fold Rises

GMFRs will be defined as the result after vaccination divided by the result before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed neutralization titers or antibody levels (later result minus earlier result) and exponentiating the mean. The associated 2-sided 95% CIs are obtained by constructing CIs using Student's t-distribution for the mean difference on the natural log scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

For SARS-CoV-2 neutralizing titers and S1-binding IgG levels and RBD-binding IgG levels, the GMRs will be provided along with associated 95% CIs. GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG levels/RBD-binding IgG levels at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

For SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age and 16 to 25 years of age, the GMRs will be provided along with associated 95% CI. The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

5.2.2.4. Geometric Mean Fold Rise Ratios

The ratios of GMFR A to GMFR B and GMFR A to GMFR C may be explored, where GMFR A is the GM of the ratio of the SARS-CoV-2 neutralizing titer at the time point after vaccination to the corresponding titer at the time point before vaccination, GMFR B is the GM of the ratio of the S1-binding IgG level at the time point after vaccination to the corresponding antibody level at the time point before vaccination, and GMFR C is the GM of the ratio of the RBD-binding IgG level at the time point after vaccination to the corresponding antibody level at the time point before vaccination.

5.2.2.5. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

5.3. Methods to Manage Missing Data

For endpoints, the missing data handling rules are described in the corresponding endpoint sections.

For the missing dates, the sponsor data standard rules for imputation will be applied (eg, partial dates for AEs will be imputed according to Pfizer standard algorithms).

Missing COVID-19 test data in Phase 2/3 for computing VE will be imputed in the sensitivity analysis. Details are included in Section 6.1.2.1.2.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Safety Endpoints

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.

- Reporting results: Descriptive statistics for each and any local reaction after each dose in each vaccine group will be presented by maximum severity across severity levels. Confirmed e-diary errors will be excluded from the analysis. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplementary Analyses

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population, analysis methodology, and appropriate reporting results. Confirmed e-diary errors will be excluded from these analyses.

- Duration (days) of each local reaction after each dose.

- Onset day of each local reaction after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose (Section 2.1).

- Analysis set: Safety population (Section 4).

- Analysis time point: Within 7 days after each dose.

- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.

- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group will be presented by maximum severity across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplementary Analyses

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after each dose.
- Onset day of each systemic event after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days after each dose will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 to 1 month after the second dose for all phases, and from Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 1 month after the second dose for all phases, Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1) for all phases and additional 3-tiered approach for Phase 2/3 (Section 3.1.1.4).
- Intercurrent events and missing data: Partial AE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: AEs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs for Phase 2/3 only. Under this approach AEs are classified into 1 of 3 tiers (Section 3.1.1.4). For both Tier 1 and Tier 2 events, 2-sided

95% CIs for the difference between the active vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[2] method will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within SOC. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs for each vaccine group.

6.1.1.3.2. Supplementary Analyses

Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 1 to 6 months after the second dose for all phases, and from Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 6 months after the second dose for all phases, Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Partial SAE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months/7 days after the second dose will be provided for each vaccine group.

6.1.1.5. Hematology and Chemistry Parameters (for Phase 1 Only)

6.1.1.5.1. Main Analyses

- Estimands: The percentage of participants with abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 (Section 2.1).
- The percentage of participants with grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2 (Section 2.1).
- Analysis set: Safety population (Section 4).

- Analysis time point: 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Analysis methodology: Descriptive statistics including counts and percentage (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive summary statistics will be provided including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.

6.1.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

6.1.2.1. COVID-19 Incidence per 1000 Person-Years of Follow-up

6.1.2.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (7 days) and all-available efficacy populations (Section 4).
- Analysis time point: At interim analyses and final analysis when the surveillance period ends.
- Analysis methodology: Assessment of VE will be performed for confirmed COVID-19 from 7 days after the receipt of the second dose of study intervention onwards, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of COVID-19 illness rate per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group after the second dose (see Appendix 3 for details on the derivation of IRR and VE). The posterior probability (ie, P[VE >30%|data]) at each interim analysis and final analysis will be computed using a beta-binomial model and a specified minimally informative beta distribution as prior (details can be found in Appendix 2).
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed in the main analyses.

- Reporting results: The point estimate of VE, 95% credible intervals using the 2.5th percentile and the 97.5th percentile, and Bayesian posterior probability of VE greater than 30% will be provided (details can be found in Appendix 2).

6.1.2.1.2. Sensitivity and Supplemental Analyses

With MAR assumption, a missing efficacy endpoint (laboratory-confirmed COVID-19 results) may be imputed based on predicted probability using the fully conditional specification method.[3] The imputation will run multiple times (up to 1000) and summary statistics similar to those used in the main analysis will be tabulated across the imputations. Other imputation methods without the MAR assumption may be explored, eg, a tipping point analysis.

All COVID-19 cases after Dose 1 may be analyzed using the Dose 1 all-available efficacy population. COVID-19 disease-related information may be summarized or listed.

Efficacy could also be assessed over a longer time period using time-to-event data analysis methods to account for censoring (participants censored when they receive other vaccines or withdraw) as well as potentially confounding factors. A Kaplan-Meier curve showing the cumulative incidence of COVID-19 cases over time may also be informative to understand the sustainability of VE.

For the assessment of efficacy in the presence of potential crossover, the established adjusting methods may be considered. For example, a rank-preserving structural failure time model may be appropriate to attempt to reconstruct data for the control arm as if crossover had not occurred, with the aim of reducing bias and allowing the vaccine effect to be assessed more accurately.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

Phase 1

The statistical analysis of immunogenicity results for Phase 1 will be primarily based on the Dose 1 and Dose 2 evaluable immunogenicity populations. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations. An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

Phase 2/3

The statistical analysis of immunogenicity results for Phase 2/3 will be based on Dose 2 evaluable immunogenicity population. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity population. An additional analysis may be performed based on the Dose 2

all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

6.2.1.1. SARS-CoV-2 Neutralizing Titers (Phase 1)

6.2.1.1.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).
  - Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination (Section 2.1).
- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2.
- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results (Section 5.2.2.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiated to transform results back to the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits (Section 5.2.2.2). Percentages of participants with ≥4-fold rise will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).
- Intercurrent events and missing data: Titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: the GMTs at each time point, GMFRs from before vaccination to each subsequent time point after vaccination, and the percentages of participants achieving ≥4-fold rise and the associated 2-sided 95% CIs from before vaccination to each time point after vaccination.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers after Dose 1 and after Dose 2 (Section 5.2.2.5).

6.2.1.2. S1-Binding IgG Levels and RBD-Binding IgG Levels (Phase 1)

6.2.1.2.1. Main Analyses

- Estimands:
  - GMCs (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).
  - Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination (Section 2.1).
- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.
- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results (Section 5.2.2.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later time point – earlier time point). Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits (Section 5.2.2.2). Percentages of participants with ≥4-fold rise will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).
- Intercurrent events and missing data: Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: the GMCs, GMFRs, and percentages of participants with ≥4-fold rise and the associated 2-sided 95% CIs will be provided for each study intervention (active/placebo) within each group before vaccination and at each time point.

Figures:

Empirical RCDCs will be provided for S1-binding IgG levels and RBD-binding IgG levels after Dose 1 and after Dose 2 (Section 5.2.2.5).

6.2.1.3. GMR of SARS-CoV-2 Neutralizing Titer to SARS-CoV-2 S1-Binding IgG Levels and RBD-Binding IgG Levels (Phase 1)

6.2.1.3.1. Main Analyses

- Estimands:
  - GMR of SARS-CoV-2 neutralizing titers to S1-binding IgG levels (Section 2.1).
  - GMR of SARS-CoV-2 neutralizing titers to RBD-binding IgG levels (Section 2.1).
- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.
- Analysis methodology: GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level or RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG levels for each participant) and exponentiating the mean (Section 5.2.2.3). Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits (Section 5.2.2.3).
- Intercurrent events and missing data: Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: The GMRs and the associated 2-sided 95% CIs will be provided for each study intervention within each group before vaccination and at each time point.

6.2.1.4. GMR of SARS-CoV-2 Neutralizing Titers in Participants 12 to 15 Years of Age to Those 16 to 25 Years of Age (Phase 2/3)

6.2.1.4.1. Main Analyses

- Estimands: GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination (Section 2.1).
- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after Dose 2.

- Analysis methodology: The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 (Section 5.2.2.3).

- Intercurrent events and missing data: Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.

- Reporting results: The GMRs and the associated 2-sided 95% CIs will be provided.

6.2.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

6.2.2.1. COVID-19 Incidence per 1000 Person-Years of Follow-up

6.2.2.1.1. Main Analyses

- Estimands:

  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy (14 days) and all-available efficacy populations (Section 4).

- Analysis time point: End of the surveillance period or at IAs if requested.

- Analysis methodology: the same method used for primary VE endpoints will be applied (Section 6.1.2.1.1).

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: the same output generated for primary VE endpoints will be provided (Section 6.1.2.1.1).

6.2.2.2. Confirmed Severe COVID-19 Incidence per 1000 Person-Years of Follow-up

6.2.2.2.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (7 days and 14 days) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period or at IAs if requested.
- Analysis methodology: the same method used for primary VE endpoints will be applied (Section 6.1.2.1.1).
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: the same output generated for primary VE endpoints will be provided (Section 6.1.2.1.1).

6.2.2.3. Confirmed COVID-19 Incidence per 1000 Person-Years of Follow-up (According to the CDC-Defined Symptoms)

6.2.2.3.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy (7 days and 14 days) and all-available efficacy populations (Section 4).

- Analysis time point: End of the surveillance period.

- Analysis methodology: Assessment of VE will be performed for centrally confirmed COVID-19 according to the CDC-defined symptoms from 7 days and from 14 days after the receipt of the second dose of study intervention onwards, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of COVID-19 illness rate according to the CDC-defined symptoms per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.2.2.4. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the N-Binding Antibody Seroconversion)

6.2.2.4.1. Main Analyses

- Estimands:

  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 (prior to 1 month after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy (1 month) and all-available efficacy populations (Section 4).

- Analysis time point: 1 month after Dose 2.

- Analysis methodology: An asymptomatic case (Appendix 4) is defined as positive N-binding antibody at a post–Dose 2 visit (eg, Visit 3, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by negative N-binding antibody at Visit 1 and negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness visit. A secondary definition will be applied without the requirement for a negative NAAT at Visit 2. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the

Clopper-Pearson method adjusted for surveillance time. The VE is demonstrated if lower bound of the 2-sided 95% CI for VE is greater than 20%.

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.2.2.5. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the Central Laboratory–Confirmed NAAT)

6.2.2.5.1. Main Analyses

- Estimands:

  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without serological or virological evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy (asymptomatic surveillance) and all-available efficacy populations (Section 4) and only participants who consented to participate in the asymptomatic surveillance.

- Analysis time point: End of the surveillance period.

- Analysis methodology: An asymptomatic case definition based on central laboratory–confirmed NAAT can be found in Appendix 5. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time. The success criterion is met if lower bound of the 2-sided 95% CI for VE is greater than 20%.

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.3. Exploratory Endpoints

6.3.1. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

6.3.1.1. COVID-19 Incidence per 1000 Person-Years of Blinded Follow-up

6.3.1.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness based on central laboratory or locally confirmed NAAT from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness based on central laboratory or locally confirmed NAAT from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants with and without evidence of infection for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (7 days) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).
- Analysis methodology: After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4. Descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time.

6.3.1.1.2. Supportive Analyses

Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. An RPSFT model may be explored to reconstruct data for the control arm.

6.3.1.2. COVID-19 Incidence per 1000 Person-Years of Follow-up

6.3.1.2.1. Main Analyses

- Estimands:
  - COVID-19 incidence based on central laboratory or locally confirmed NAAT from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second BNT162b2 vaccination) who received BNT162b2 at initial randomization or subsequently (Section 2.1).
  - COVID-19 incidence based on central laboratory or locally confirmed NAAT from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection who received BNT162b2 at initial randomization or subsequently (Section 2.1).
- Analysis set: Evaluable efficacy (7 days) and all-available efficacy populations (Section 4). For participants who were randomized to placebo and subsequently received BNT162b2 after being eligible according to local or national recommendations or at approximately Visit 4, the time of receipt of BNT162b2 will be reconsidered as baseline. All rules for determining evaluable efficacy and all-available efficacy populations will be similarly applied.
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second BNT162b2 vaccination will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: Incidence rate and the associated 2-sided 95% CIs, and Kaplan-Meier cumulative incidence curve will be provided.

6.3.1.3. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Blinded Follow-up (According to the N-Binding Antibody Seroconversion)

6.3.1.3.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection through the blinded follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past

SARS-CoV-2 infection or confirmed COVID-19 during the study for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).
- Analysis time point: 6 months after Dose 2.
- Analysis methodology: VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.3.1.4. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the N-Binding Antibody Seroconversion)

6.3.1.4.1. Main Analyses

- Estimands:
  - Incidence of asymptomatic SARS-CoV-2 infection through the entire study of follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 during the study.
- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).
- Analysis time point: 1, 6, 12, and 24 months after Dose 2.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic infection will be provided for participants who received BNT162b2.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: Incidence rate and the associated 2-sided 95% CIs will be provided.

6.3.1.5. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the Central Laboratory–Confirmed NAAT)

6.3.1.5.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence of past infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (asymptomatic surveillance) and all-available efficacy populations (Section 4) and only participants who are consented to participate in the asymptomatic surveillance.
- Analysis time point: End of the surveillance period.
- Analysis methodology: VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.3.2. Immunogenicity Endpoints (for Phase 2/3 Only)

6.3.2.1. SARS-CoV-2 Neutralizing Titers, and Full-length S-Binding or S1-Binding IgG Levels

6.3.2.1.1. Main Analyses

- Estimands:
  - GMTs/GMCs (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).
- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results Section 5.2.2.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later time point – earlier time point). Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits (Section 5.2.2.2). Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Titers/concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.

- Reporting results: the GMTs/GMCs at each time point and GMFRs from before vaccination to each subsequent time point after vaccination, and the empirical RCDCs after Dose 1 and after Dose 2, will be provided.

6.3.2.1.2. Additional Exploratory Analyses

The above analyses will be performed by baseline SARS-CoV-2 status (positive or negative).

6.3.2.2. Serological Responses in Participants With Confirmed COVID-19, Confirmed Severe COVID-19, and SARS-CoV-2 Infection Without Confirmed COVID-19

The analyses described above for exploratory immunogenicity endpoints may be applied to the participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19.

6.3.3. Additional Analysis

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point (Section 5.2.2.4).

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2" will be summarized descriptively.

AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations or at approximately Visit 4.

All severe COVID-19 cases occurring after Dose 1 will be summarized descriptively.

6.4. Subgroup Analysis

Subgroup analyses based on age, race, ethnicity, sex, country, and baseline SARS-CoV-2 status will be performed on all primary safety and efficacy endpoints (as supplemental analyses) for Phase 2/3.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age group, sex, race, ethnicity, and classification of BMI will be summarized for the safety population for each vaccine group and overall.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a SOC and PT according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group for the overall safety population.

The number and proportion of participants with comorbidities that increase the risk for severe COVID-19 illness will be summarized by each vaccine group.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (Doses 1 and 2), who completed the follow-up visits (1 month after the second dose), and who withdrew before each follow-up visit along with the reasons for withdrawal will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately along with the reasons for exclusion, by vaccine group.

Participants follow-up time after completion of vaccinations will be summarized by vaccine group.

6.5.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-specified time frames will be tabulated separately for each time point.

6.5.2.3. E-Diaries

The participants who were vaccinated and completed e-diaries after each dose will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1.1 and Section 6.1.1.2, the summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary, and transmitting the e-diary for any day in the required reporting period, by as-received vaccine group for each dose.

The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for all randomized participants. The denominator for the percentages is the total number of randomized participants in the given vaccine group or overall.

In addition, the relation of randomized vaccine to actual vaccine received will be presented as a cross tabulation of the actual vaccine received versus the randomized vaccine.

A listing of participants showing the randomized vaccine and the vaccine actually received at each dose will be presented.

6.5.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification. All vaccines received within 28 days before Dose 1 will be listed. The number and percentage of participants receiving each concomitant vaccine after Dose 1 will be tabulated by vaccine group. A summary will be provided for the interval between Dose 1 and 1 month after the second dose. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analyses

Local reaction, systemic event, AE, and SAE summaries and analyses are described under Primary Endpoint(s) (Section 6.1).

7. ANALYSES TIMING

7.1. Introduction of Interim Analysis

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis can be found in Appendix 2.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint, and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%), which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 11 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 11. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine:placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 12 and Table 13 for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 12. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 13. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of study intervention onwards.

Only the first primary endpoint will be analyzed at an IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints will be evaluated sequentially in the following order by the same method used for the evaluation of primary VE endpoints: (1) confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and (2) in all participants; (3) confirmed severe COVID-19 occurring from 7 days after the second dose in participants without evidence of infection and (4) in all participants; (5) confirmed severe COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and (6) in all participants.

Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

7.2. Interim Analyses and Summaries

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

- Complete safety and efficacy analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

7.2.1. Data Monitoring Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BLQ	below the level of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DBP	diastolic blood pressure
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
FiO_2	fraction of inspired oxygen
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HR	heart rate
IA	interim analysis
ICD	informed consent document
ICU	intensive care unit
IgG	immunoglobulin G
IND	indeterminate
IRC	internal review committee
IRR	illness rate ratio
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable

Abbreviation	Term
NAAT	nucleic acid amplification test
non-S	nonspike protein
PaO_2	partial pressure of oxygen, arterial
POS	probability of success
PT	preferred term
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RPSFT	rank-preserving structural failure time
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization

Appendix 2. Details for Bayesian Design

Bayesian group sequential design will be implemented in the Phase 3 for this study.

Notation

(1) Let VE be vaccine efficacy, θ be the case rate (number of cases in the active vaccine group divided by the total number of cases), T_1 be the total person-time in the active vaccine group, T_0 be the total person-time in the placebo group, and r be the ratio of T_1 and T_0, ie, $r = T_1/T_0$. Note that $\theta = \frac{r(1-VE)}{r(1-VE)+1}$ and $VE = 1 - \frac{\theta}{r(1-\theta)}$.

(2) Let p be the posterior probability of VE greater than or equal to 30% given the observed data on subset of enrolled participants, ie:

$$p = \Pr(VE > 30\% \mid \text{observed data from subset of enrolled participants})$$

$$= \Pr\left(\theta < \frac{r(1-30\%)}{r(1-30\%)+1} \mid \text{observed data from subset of enrolled participants}\right)$$

Under the assumption that the numbers of cases in both vaccine groups, s_1 and s_0 for cases in the active vaccine group and cases in the placebo group, respectively, follow a Poisson distribution with parameter λ_1 (incidence rate) for the active vaccine group and λ_0 for the placebo group, we can assume that s_1 is binomially distributed with Binomial (s, θ), conditional on s, the total number of cases, and with $\theta = T_1 \lambda_1 / (T_1 \lambda_1 + T_0 \lambda_0)$.

A minimally informative beta prior, Beta(0.700102, 1) is selected as the prior distribution of θ. The prior distribution is chosen such that the mean is equal to 0.4118 corresponding to VE = 30% which can be considered pessimistic. Meanwhile, the prior allows for considerable uncertainty, ie, 95% credible interval for θ is (0.005, 0.964) corresponding to 95% credible interval, (-26.2, 0.995), for VE.

Decision Algorithm for Efficacy

At certain interim analysis and final analysis, let n be the total number of observed cases and n_v be the number of observed cases from the vaccine group. For beta-binomial model, the posterior distribution of θ will be derived as Beta($\alpha' = 0.700102 + n_v$, $\beta' = 1 + n - n_v$). At each interim and final analysis p will be used for efficacy decision making in the following way:

(a) At interim analyses, efficacy is declared if $p > 99.50\%$.

(b) At final analysis, efficacy is declared if $p > 98.60\%$.

In participants without evidence of infection prior to 7 days after the second dose, IAs will be performed after accrual of at least 62, 92, and 120 cases, and final analysis will be performed after accrual of at least 164 cases.

Based on the criterion (b), at final analysis, efficacy will be declared if there are less than or equal to 53 cases observed in the vaccine group among the total number of 164 cases.

Bayesian 95% credible interval for θ can be calculated using the 2.5th percentile and the 97.5th percentile of posterior distribution, ie, Beta(α'=0.700102 + n_v , β'=1 + n - n_v). Thus, the 95% credible interval for VE can be obtained correspondingly due to the relationship between VE and θ, where $VE = 1 - \frac{\theta}{r(1-\theta)}$.

Decision Algorithm for Futility

Let Y be the random variable for the number of cases in the vaccine group at the final analysis. At certain interim analysis given the total number of observed cases n and the number of observed cases from the vaccine group n_v, the posterior probability of success q can be expressed as:

q = Pr (Y ≤ 53 | observed data, ie, n and n_v, from subset of enrolled participants)

q can be calculated analytically using posterior predictive distribution of Y, ie, Beta-Binomial distribution with parameters (n', α', β'). The probability mass function of the posterior predictive distribution is:

$$\Pr(Y = y | n', \alpha', \beta') = \binom{n'}{y} \frac{B(y + \alpha',\ n' - y + \beta')}{B(\alpha', \beta')}$$

Thus the posterior probability of success at the interim analysis can be calculated as:

q = Pr (Y ≤ 53 – n_v | n' = 164 – n, α'=0.700102 + n_v , β'=1 + n - n_v)

At interim analyses, futility is declared if q < 5.0%.

Appendix 3. IRR and VE Derivation

COVID-19 Case Definition

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

Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

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

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

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

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

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

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Surveillance Times

Fundamental to this VE trial is the surveillance for cases satisfying various endpoints within each participant that may occur during the trial. Endpoint and participant combinations where surveillance is applicable require identification of the start and the end of the surveillance period in order to determine the participant-level endpoint surveillance time. For all VE-related endpoints in this study, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy (7 days)	Dose 2 + 7 days
Dose 2 all-available efficacy	Dose 2 + 7 days
Evaluable efficacy (14 days)	Dose 2 + 14 days
Dose 2 all-available efficacy	Dose 2 + 14 days
Dose 1 all-available efficacy	Dose 1

For all VE-related endpoints in this study, the end of a surveillance period for each participant is the earliest of the following events:

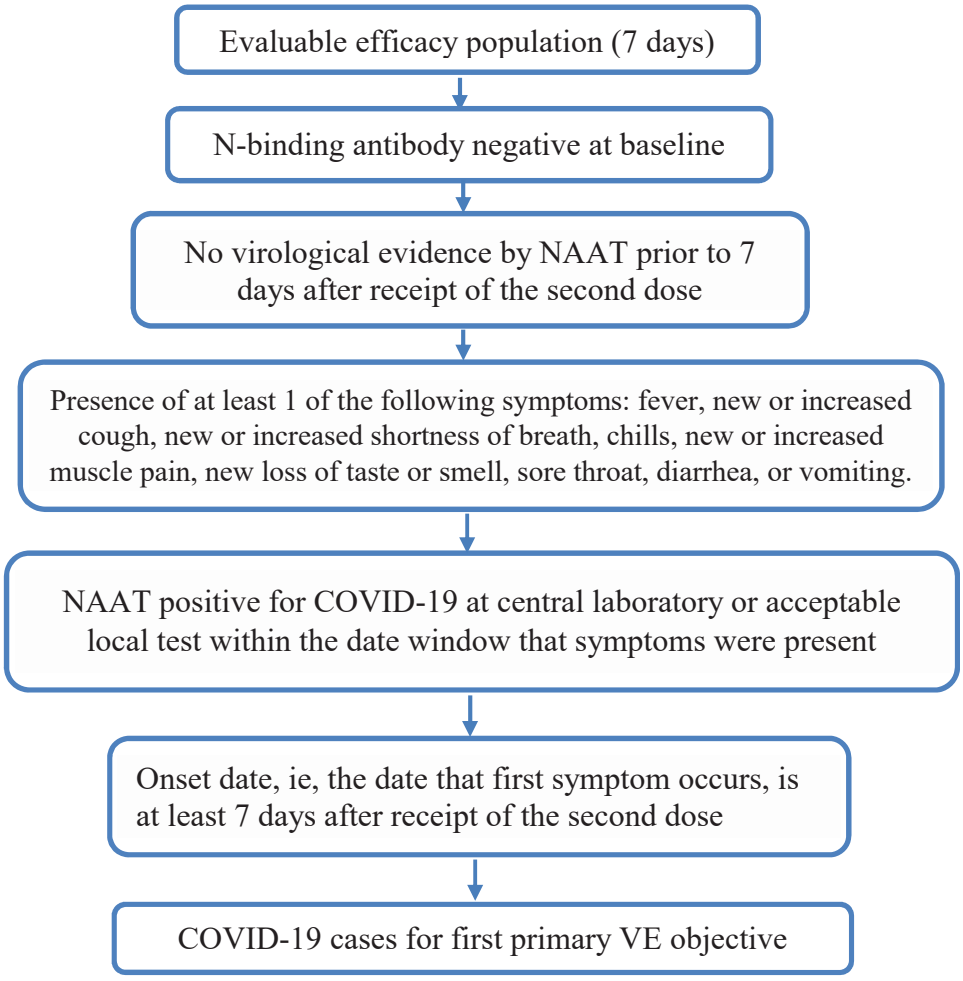
- When the first COVID-19 case occurs.
- When the participant's end of the study occurs due to, eg withdrawal or death or trial completion and etc.
- When the participant has first important protocol violation.

Specific information regarding VE-related endpoint surveillance start and end times by endpoint will be provided in Analysis and Reporting Plan specification documents.

Once the COVID-19 cases and surveillance period have been identified, VE can be calculated as $100 \times (1 - IRR)$, where IRR is the ratio of confirmed COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group.

Flowchart

1. The flowchart for deriving the COVID-19 cases included below for the first primary endpoints in evaluable efficacy participants with no serological or virological evidence of past SARS-CoV-2 infection:



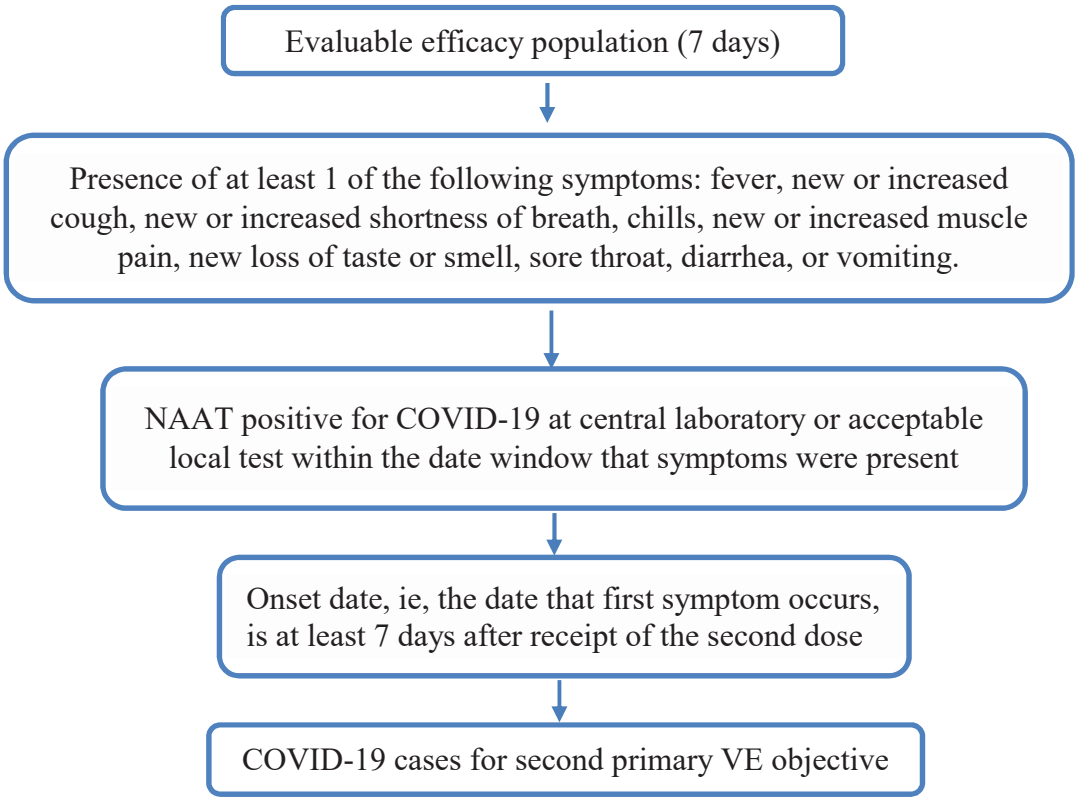
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

b. Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)

c. Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

2. The flowchart for deriving the COVID-19 cases included below for the second primary endpoints in evaluable efficacy participants:



The flowcharts for the first 2 secondary vaccine efficacy endpoints are similar to the primary endpoints except that the case counting starts from 14 days after receipt of the second dose.

Appendix 4. Asymptomatic Case Based on N-Binding Antibody Seroconversion

Asymptomatic Case Definition

An asymptomatic case is defined as positive N-binding antibody at a post–Dose 2 visit (eg, Visit 3, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by negative N-binding antibody at Visit 1 and negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness visit. A secondary definition will be applied without the requirement for a negative NAAT at Visit 2.

Surveillance Times

For the asymptomatic case based on N-binding antibody seroconversion, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy (1 month)	Dose 2
Dose 2 all-available efficacy	Dose 2
Dose 1 all-available efficacy	Dose 1

The end of a surveillance period for each participant is the date of the scheduled post–Dose 2 visit (eg, Visit 3) N-binding antibody result. Participants without N-binding antibody result at the scheduled visit will be excluded. For the analysis based on the evaluable efficacy population, participants who had important protocol violations prior to that visit will also be excluded.

Appendix 5. Asymptomatic Case Based on Central Laboratory–Confirmed NAAT

Asymptomatic Case Definition

An asymptomatic case is defined as positive NAAT without COVID-19 symptoms in participants who are consented to participate in the asymptomatic surveillance and without (or with) serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

Surveillance Times

The start-of-surveillance time is the start of the asymptomatic surveillance period.

The end of a surveillance period for each participant is the earliest of the following events:

- When the first positive NAAT occurs.
- When the last NAAT result is available.
- When the first COVID-19 symptom occurs.
- When the participant's end of the asymptomatic surveillance period occurs because of the participant's end of participation in the study (withdrawal, death, trial completion, etc), unblinding because the participant is eligible for receipt of BNT162b2 according to local or national recommendations, other reason for unblinding, etc.
- When the participant has his or her first important protocol violation.