nature research

https://doi.org/10.1038/s41586-020-2639-4

Supplementary information

Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults

In the format provided by the authors and unedited

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 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:	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**

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

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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 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, "heads up," 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 may be tested in this study are therefore:

BNT162b1 ([redacted]): a modRNA encoding the RBD;

BNT162b2 ([redacted]): 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 potential efficacy of these 2 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), 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 serum neutralizing titers
	• 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	SARS-CoV-2 S1-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 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 – illness rate ratio) [ratio of active vaccine to placebo]	• SARS-CoV-2 serum neutralizing titers • SARS-CoV-2 S1-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 2 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 various 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 28 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 420 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 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 18 to 85 years of age [stratified as ≤55 or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): 10 µg, 20 µg, 30 µg, 50 µg, 100 µg

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg, 50 µg, 100 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

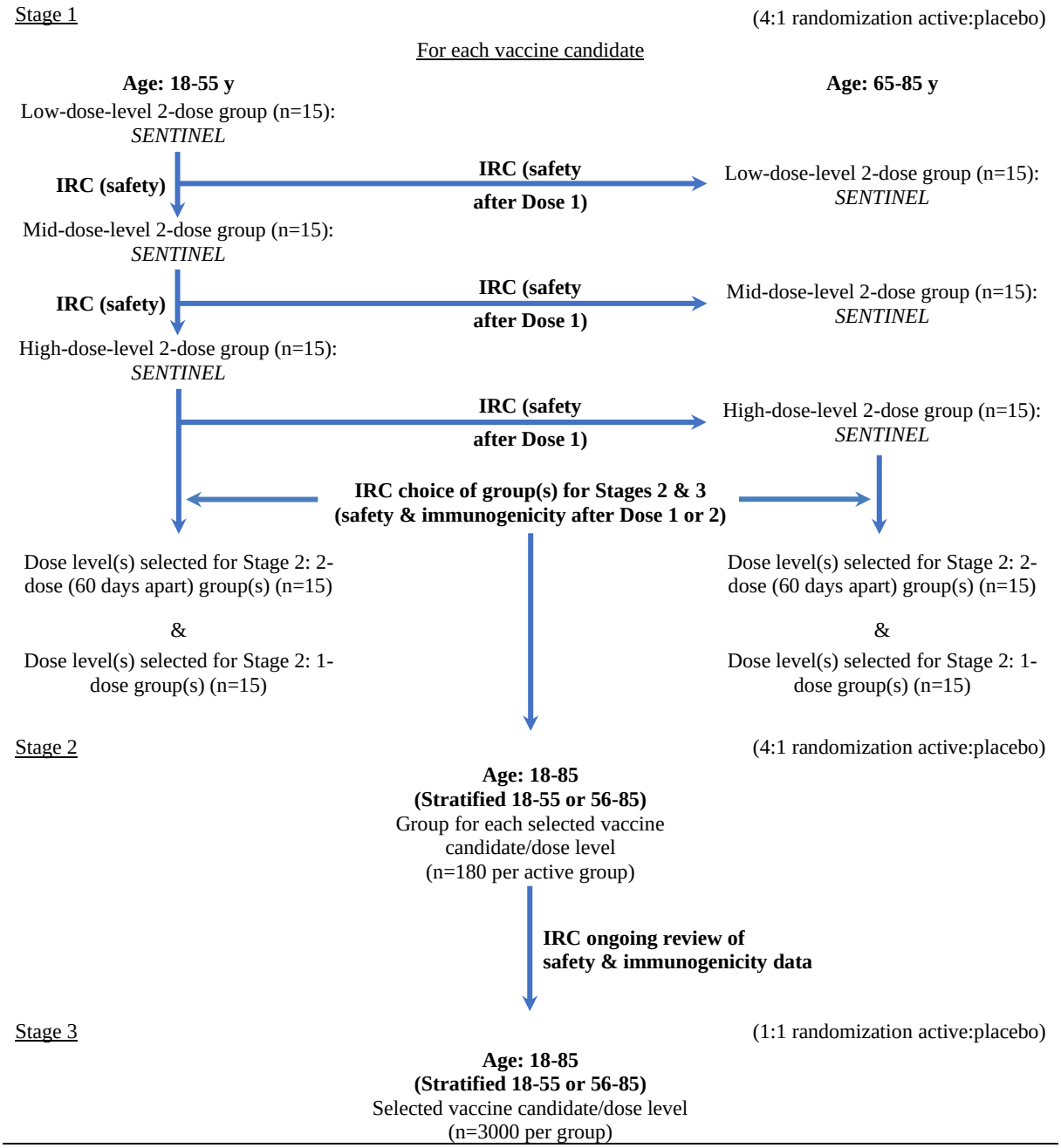
The study sample size for the first 2 stages of the study is not based on any statistical hypothesis testing. For the third stage, with assumptions of a true vaccine efficacy (VE) of 70%, 53 cases of COVID-19 will provide 90% power to conclude true VE >20%. This would be achieved with 3000 participants 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 serum neutralizing titers, SARS-CoV-2 S1-specific binding antibody levels, and RBD-specific binding antibody levels at the various time points.

For the secondary efficacy objective, VE is defined as VE = 100 × (1 – IRR), where IRR is the illness 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 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**	**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 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**	**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 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**	**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 + optional[d] ~170 mL	~50 mL + optional[d] ~170 mL	~50 mL + optional[d] ~170 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								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		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 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**	**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**
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		
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.

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 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**	**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**

d. 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. 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	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	~25 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							
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X								
Provide participant with 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
Collect e-diary or assist the participant to delete application							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**
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	~25 mL		~25 mL		~25 mL	~25 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						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide participant with 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
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 2 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.

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, "heads up," prefusion spike glycoprotein (P2 S) ([redacted]), or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) ([redacted]). The 2 SARS-CoV-2 vaccine candidates that may be tested in this study are therefore:

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

- **BNT162b2** ([redacted]): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

2.2.1. Clinical Overview

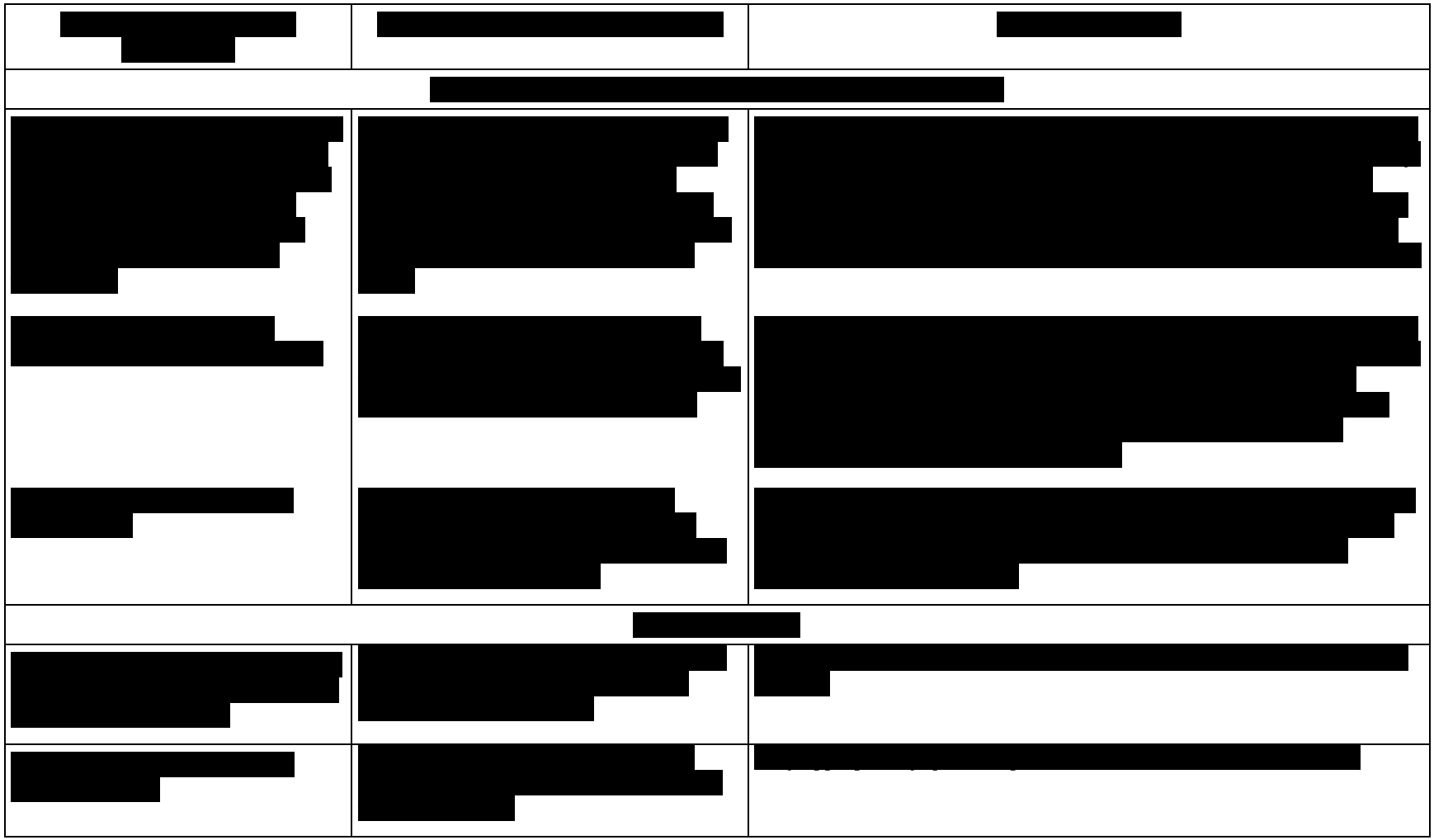
BNT162 vaccines have not been administered to humans before and thus there are no previous clinical data with these specific vaccines. However, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials[6] and recent published results from clinical trials 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.

[redacted]



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 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 S1-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 serum neutralizing titers to the geometric mean 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 – illness rate ratio) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up

Objectives	Estimands	Endpoints
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 2 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 various 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 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.

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 28 potential groups are foreseen; if all groups are fully enrolled, this corresponds to a total of 420 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 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 [redacted] modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses [redacted] doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

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
    - 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

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 (except for sentinel participants in Stage 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Sentinel participants in Stage 1 only:** Regular receipt of inhaled/nebulized corticosteroids.

15. 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:

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

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

Diagnostic Assessments:

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

19. **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.)

20. **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.

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

Other Exclusions:

22. 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 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 18 to 85 years of age [stratified as ≤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, 50 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 µg, 20 µg, 30 µg, 50 µg, 100 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**		
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)
b1-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	20 µg	(n=12) (n=3)	BNT162b1 Placebo	20 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)
b1-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b1 Placebo	50 µg	(n=12) (n=3)	BNT162b1 Placebo	50 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)
b2-20-2-Y (Sentinel) [modRNA 20 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	20 µg	(n=12) (n=3)	BNT162b2 Placebo	20 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)
b2-50-2-Y (Sentinel) [modRNA 50 µg (2 doses)]	15	18 to 55	BNT162b2 Placebo	50 µg	(n=12) (n=3)	BNT162b2 Placebo	50 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)
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)
b1-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	20 µg	(n=12) (n=3)	BNT162b1 Placebo	20 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)
b1-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b1 Placebo	50 µg	(n=12) (n=3)	BNT162b1 Placebo	50 µg	(n=12) (n=3)
b1-100-2-O (Sentinel)	15	65 to 85	BNT162b1 Placebo	100 µg	(n=12) (n=3)	BNT162b1 Placebo	100 µg	(n=12) (n=3)

Table 1. Potential Groups in Stage 1

Groups	N	Age Group (Years)	Dose 1			Dose 2		
[modRNA 100 µg (2 doses)]								
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)
b2-20-2-O (Sentinel) [modRNA 20 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	20 µg	(n=12) (n=3)	BNT162b2 Placebo	20 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)
b2-50-2-O (Sentinel) [modRNA 50 µg (2 doses)]	15	65 to 85	BNT162b2 Placebo	50 µg	(n=12) (n=3)	BNT162b2 Placebo	50 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)
Single-Dose Groups			**Day 1**			**Day 22**		
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)
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)
2-Dose Groups (Longer Schedule)			**Day 1**			**Day 61**		
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)
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)

Abbreviations: modRNA = nucleoside-modified messenger ribonucleic acid; TBD = to be determined.

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)	[redacted]/0.5 mL	[redacted]/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-,30-, 50-, 100-µg	10-, 20-,30-, 50-, 100-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.

6.1.1. Administration

Participants will receive 1 dose 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. 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.

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 inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Stage 1 sentinel cohorts.

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 Stage 1 sentinel cohorts – 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.

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. Select participants in the sentinel cohorts of Stage 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, 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 serum neutralization assay
- SARS-CoV-2 S1-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.

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 Stage 1 sentinel cohorts (see Section 8.11.1.1) to determine eligibility.

Serum obtained from the additional ~170-mL blood sample from select participants in the sentinel cohorts of Stage 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.

8.2. 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 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. 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 a reactogenicity e-diary through an application (see Section 8.14) 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 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 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 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 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	2.0 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 3.

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 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 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 4.

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 4. 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. 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 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.

BNT162 RNA platforms (ie, a, b, and c) will be evaluated for contribution to stopping rules individually; vaccine candidate dose levels within a 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 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 non–sentinel-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 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 8.2.5.

- 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.

- 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 8.2.5.

- 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 (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 8.2.5.

- 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 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: (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 (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. 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 (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.

8.11.1.11. 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.
- 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. 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 25 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 (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.

8.11.2.2. 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 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 8.2.5.
- 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 25 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 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.

8.11.2.3. 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 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.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 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.

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 25 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.

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 25 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.

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

- Collect a blood sample (approximately 25 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.

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

- Collect a blood sample (approximately 25 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.

8.11.3. 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 25 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 (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.

8.11.3.2. 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 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 8.2.5.
- 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 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.

8.11.3.3. 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 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.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample (approximately 25 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.

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 (this could be via the COVID-19 illness e-diary) 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 25 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.

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

- Collect a blood sample (approximately 25 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.

8.12. 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 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 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. 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;
- 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.

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 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 and the study site staff will be established. The participant 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 to report whether or not he or she has experienced symptoms that could represent a potential COVID-19 illness (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.

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.

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 illness rate ratio, the calculated ratio of the COVID-19 illness 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 illnesses, only the first COVID-19 confirmed case 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 28 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 420 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 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.

Population	Description
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.

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 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-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 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody levels and RBD-specific binding antibody 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 to the original scale. Two-sided CIs will be obtained by

Endpoint	Statistical Analysis Methods
	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 serum neutralizing titers and SARS-CoV-2 S1-specific binding antibody and RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific antibody levels and RBD-specific binding antibody 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 serum neutralizing titer to SARS-CoV-2 S1-specific antibody and SARS-CoV-2 RBD-specific binding antibody** For SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-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 GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-specific

Endpoint	Statistical Analysis Methods
	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 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 serum neutralizing titers, SARS-CoV-2 S1-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 illness 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

Endpoint	Statistical Analysis Methods
	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 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 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 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 S1-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 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.

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.

[redacted]

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. [redacted]

[redacted]

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 (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

Table 6. Laboratory Abnormality Grading Scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
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 <u>Meeting</u> 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	illness 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
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
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	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

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