Protocol

Protocol for: Zou J, Kurhade C, Patel S, et al. Neutralization of BA.4–BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with bivalent vaccine. N Engl J Med. DOI: 10.1056/NEJMc2214916

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

Improved Neutralization of Omicron BA.4/5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with Bivalent BA.4/5 Vaccine

This supplement contains the following items:

AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2 OBSERVER-BLIND STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BIVALENT BNT162b RNA-BASED VACCINE CANDIDATE AS A BOOSTER DOSE IN COVID-19 VACCINE–EXPERIENCED HEALTHY ADULTS

Study Sponsor:	BioNTech
Study Conducted by:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162 RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT/CTIS Number:	2022-002008-19
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	EMEA-002861-PIP02-20-M03
Protocol Number:	C4591044
Phase:	2

Brief Title:

A Study to Learn About a New COVID-19 RNA Vaccine Candidate as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Adults

Document History

Document	Version Date
Original protocol	14 June 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Interventional, Randomized, Active-Controlled, Phase 2 Observer-Blind Study to Investigate the Safety, Tolerability, and Immunogenicity of a Bivalent BNT162b RNA-Based Vaccine Candidate as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Adults.

Brief Title:

A Study to Learn About a New COVID-19 RNA Vaccine Candidate as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Adults

Regulatory Agency Identification Numbers:

US IND Number:	19736
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ClinicalTrials.gov ID:	Not available
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Phase:	2

Rationale:

BNT162b2 (Comirnaty®) is an RNA-based vaccine that, as of April 2022, has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 140 countries for the prevention of COVID-19 caused by SARS-CoV-2. The vaccine encodes the spike protein with a modRNA, is encapsulated in RNA-LNPs, and has demonstrated potent immunogenicity, high vaccine efficacy, and a favorable safety profile in Phase 1, 2, and 3 human trials, as well as in real-world usage. Since the start of the pandemic, several VOCs have emerged, causing surges in infection rates, despite uptake of vaccines. Currently, the SARS-CoV-2 Omicron variant B.1.1.529 and its sublineages BA.1.1, BA.2.12.1, and BA.2 are dominant in many countries and within the US are responsible for nearly all sequenced COVID-19 cases as of 28 May 2022. Moreover, studies have demonstrated that the effectiveness of BNT162b2 against SARS-CoV-2 infection and COVID-19 disease wanes over a period of months, particularly in the context of VOCs.

In light of the waning effectiveness of the primary 2-dose series of BNT162b2 as well as the existence of VOCs with cumulative mutations in the spike protein that are resilient to the existing immune response, particularly Omicron, development of an enhanced bivalent

vaccine that could generate an improved immune response, including against VOCs, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate in this study an enhanced BNT162b RNA-based vaccine candidate, BNT162b5 Bivalent (WT/OMI BA.2), consisting of a modified version of the SARS-CoV-2 spike protein mRNA, targeting the ancestral strain of the virus, in combination with mRNA encoding the spike protein of the Omicron variant (BA.2 sublineage).

Objectives, Endpoints, and Estimands:

Objectives	Estimands	Endpoints
Primary Safety		
To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Primary Immunogenicity		
To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFRs from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)-neutralizing titers • SARS-CoV-2 Omicron (BA.1)-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
Exploratory		
To describe the immune response to emerging VOCs		• SARS-CoV-2 neutralizing titers for Omicron sublineages and VOCs not already specified

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Overall Design:

This study is a randomized, active-controlled, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a new bivalent vaccine at the 30-µg dose level.

Participants will be randomized at a ratio of 1:1 to receive a single dose of 1 of the 2 study interventions. Participants will be stratified by the number of months since the last dose of the COVID-19 vaccine received prior to entering the study (3-6 months or >6 months).

Number of Participants:

Approximately 200 participants will be enrolled in the study.

Study Population:

The inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participants 18 through 55 years of age at randomization.

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

Participant and Disease Characteristics:

2. Participants willing and able to comply with all scheduled visits/contacts, investigational plan, laboratory tests, 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. Participant is capable of giving signed informed consent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusion Criteria:

5. Participants who have received 1 booster dose of a US-authorized COVID-19 vaccine, with the last prior dose being 90 or more days before Visit 1 (Day 1).

   Note: Documented confirmation of prior COVID-19 vaccines received must be obtained prior to randomization. All prior COVID-19 vaccines must be authorized for use in the US.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

5. 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.

Prior/Concomitant Therapy:

6. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment through conclusion of the study.

   Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease) or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

Prior/Concurrent Clinical Study Experience:

8. Participation in other studies involving a study intervention within 28 days before randomization. Anticipated participation in other studies within 28 days after receipt of study intervention in this study.

Other Exclusion Criteria:

9. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Study Arms and Duration:

For the purposes of this protocol, study intervention refers to:

- BNT162b5 Bivalent (WT/OMI BA.2)

  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)

- BNT162b2 Bivalent (WT/OMI BA.1)

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

The study duration for each participant will be approximately 6 months.

Study Interventions		
Intervention Name	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2]) Preformulated as a single vial (no dilution required)	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Unit Dose Strength(s)	100 µg/mL	100 µg/mL

Study Interventions		
Dosage Level(s)	30 µg (15 µg BNT162b5 Wild Type and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental and active comparator
IMP or NIMP/AxMP	IMP	IMP

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Study Arms		
Arm Title	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Arm Type	Experimental	Experimental and active comparator
Arm Description	Participants will receive 30 µg of BNT162b5 Bivalent (WT/OMI BA.2) at Visit 1.	Participants will receive 30 µg of BNT162b2 Bivalent (WT/OMI BA.1) at Visit 1.

Statistical Methods:

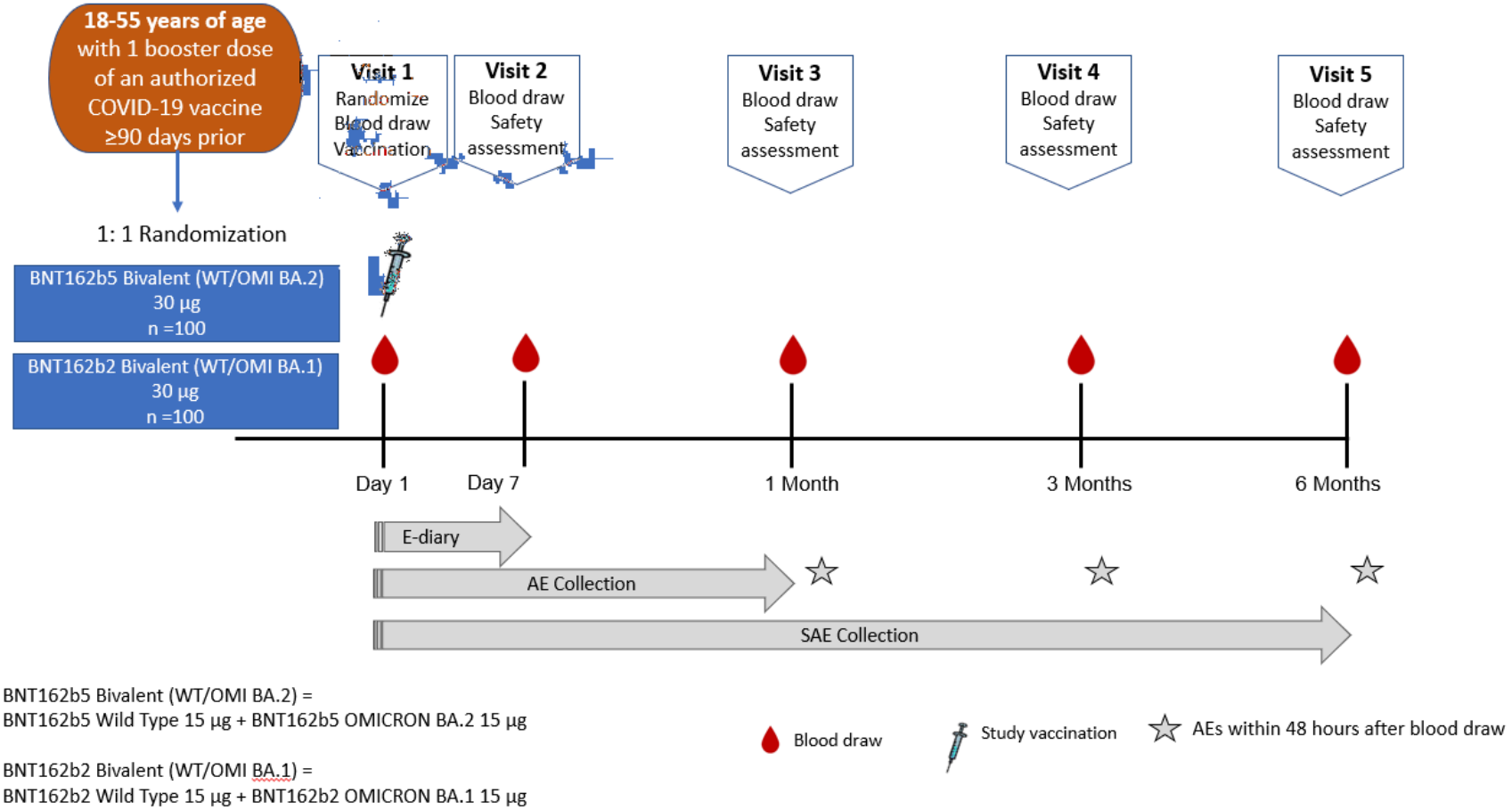
The sample size is not based on any statistical hypothesis testing. All objectives are descriptive. The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group. The primary immunogenicity objectives will be evaluated descriptively by GMT, GMFR, and percentage of participants with seroresponse of SARS-CoV-2 neutralizing titers at the various time points.

Ethical Considerations:

The available safety and immunogenicity data from ongoing Pfizer-BioNTech clinical trials and real-world effectiveness and safety data, combined with available nonclinical data with BNT162 vaccines and data from nonclinical and clinical trials with the same or related RNA components or antigens, support a favorable benefit/risk profile and support clinical development of BNT162b5 Bivalent (WT/OMI BA.2). Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

- As BNT162b5 Bivalent (WT/OMI BA.2) and BNT162b2 Bivalent (WT/OMI BA.1) have the same modRNA and LNP platform as BNT162b2, their safety profiles are expected to be similar to that of BNT162b2. Based on the experience with BNT162b2, the potential risks for BNT162b2 include the following:
    - Local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic reactions, such as fever, fatigue, headache, chills, muscle pain, and joint pain.
    - Very rare cases of myocarditis and pericarditis have been reported after authorization in recipients of BNT162b2.
    - Cases of anaphylaxis have been reported; however, the frequency is not estimable from the available data.
- The study procedure-related risks include:
    - Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.
    - Venipuncture will be performed during the study.
- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.

1.2. Schema



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. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, study visits, blood sample collection/analysis or other procedures may be halted or discontinued.

						Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Visit 1 may be performed over 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day**
Obtain informed consent	X					
Assign participant number	X					If participant is from a prior Pfizer COVID-19 study, record the participant number of the prior study in the CRF
Obtain demography and medical history data (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result)	X					
Obtain documentation of all prior COVID-19 vaccines	X					Record details in the prior COVID-19 vaccination CRF
Urine pregnancy test (if appropriate)	X					Refer to Section 8.3.5
Confirm use of contraceptives (if appropriate)	X	X	X			Refer to Section 5.3.1
Measure height and weight	X					
Perform clinical assessment	X	X	X	X	X	Including, if indicated, a physical examination (Section 8.3.1)

						Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Visit 1 may be performed over 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day**
Record nonstudy vaccine information	X	X	X	X	X	Refer to Section 6.9
Record prohibited medication use		X	X	X	X	Refer to Section 6.9.1
Confirm eligibility	X					
Measure body temperature	X					
Review temporary delay criteria	X					
Nasal (midturbinate) swab for SARS-CoV-2 NAAT	X					
Blood sample for immunogenicity assessment	~50 mL	~20 mL	~50 mL	~20 mL	~20 mL	Blood sample collection may be halted or discontinued upon notification by Pfizer
Obtain randomization number using the IRT system	X					
Obtain the participant's vaccine vial allocation using the IRT system	X					
Administer study intervention	X					Refer to Section 6.1.1
Assess acute reactions for at least 30 minutes after study intervention administration	X					
Explain participant communication methods (including for e-diary completion and severe reactogenicity symptoms), assist the participant with downloading the app or issue provisioned device, if required	X					
Provide thermometer and measuring device	X					
Ask/remind the participant to contact the site if participant experiences any severe (Grade 3) reactogenicity symptoms	X	X				

						Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Visit 1 may be performed over 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day**
Ask/remind the participant to contact the site if a medically attended event or hospitalization occurs	X	X	X	X		
Ask/remind the participant to contact site immediately if participant experiences any symptoms of acute chest pain, shortness of breath, or palpitations	X	X				Refer to Section 8.10.8
Review e-diary data (daily review is optimal during the active diary period)	←	→				If Visit 2 occurs on Day 6, continue to review e-diary data through Day 7
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X			
Collect AEs and SAEs as appropriate	X	X	X	X	X	Includes nonserious AEs through Visit 3, any AEs occurring up to 48 hours after a blood draw, and SAEs through the end of study (see Section 8.4.1)
Assist the participant to delete the e-diary application or collect the provisioned device			X			If the e-diary period ended at Visit 2, this activity may be done at Visit 2.

Abbreviations: CRF = case report form; IRT = interactive response technology; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2. INTRODUCTION

BNT162b2 (Comirnaty) is an RNA-based vaccine that, as of April 2022, has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 140 countries for the prevention of COVID-19 caused by SARS-CoV-2.[1] In the US, it has been fully licensed for use in individuals 16 years of age and above as of 23 August 2021.[2] A third dose of BNT162b2 has been granted EUA in the US and many other countries to reduce the risk of infection in light of emerging new SARS-CoV-2 variants and increasing incidence of COVID-19 disease.[3,4,5] In the US, a fourth dose has been granted EUA for individuals 50 years of age and older as well as for individuals 12 years of age and older with certain kinds of immunocompromising conditions.[6]

The vaccine encodes the spike protein with a modRNA, is encapsulated in RNA-LNPs, and has demonstrated potent immunogenicity, high vaccine efficacy, and a favorable safety profile in Phase 1, 2, and 3 human trials,[7] as well as in real-world usage.[8] As SARS-CoV-2 continues to circulate at very high levels,[9] Pfizer/BioNTech are investigating next-generation, RNA-based COVID-19 vaccines, including BNT162b5 Bivalent (WT/OMI BA.2), to further protect against COVID-19 caused by emergent and potentially more antigenically diverse VOCs.

2.1. Study Rationale

Since the start of the pandemic, several VOCs have emerged, causing surges in infection rates, despite uptake of vaccines. Currently, the SARS-CoV-2 Omicron variant B.1.1.529 and its sublineages BA.1.1, BA.2.12.1, and BA.2 are currently dominant in many countries and within the US are responsible for nearly all sequenced COVID-19 cases as of 28 May 2022, with BA.2 and BA.2.12.1 accounting for close to 94% of sequenced COVID-19 cases.[10] The UK Health Security Agency reports that the effectiveness of ChAdOx1-S, BNT162b2, and mRNA-1273 (pooled analysis) against hospitalization is 88% (range, 78%-93%) for the Omicron variant 2 or more weeks after a booster dose.[11] However, other studies have demonstrated that the effectiveness of BNT162b2 against SARS-CoV-2 infection and COVID-19 disease wanes over a period of months, particularly in the context of VOCs.[12,13,14] In light of the waning effectiveness of the primary 2-dose series of BNT162b2 as well as the existence of VOCs with cumulative mutations in the spike protein that are resilient to the existing immune response, particularly the Omicron variant, development of an enhanced bivalent vaccine that could generate an improved immune response, including against VOCs, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate in this study a vaccine candidate, BNT162b5 Bivalent (WT/OMI BA.2), which is an enhanced version of BNT162b2 Wild Type (ancestral strain, Wuhan-Hu-1; USA-WA1/2020) combined with BNT162b5 OMICRON (BA.2 sublineage), which has been designed to produce an improved antibody response against SARS-CoV-2. BNT162b5 Bivalent (WT/OMI BA.2) uses the same modRNA platform, manufacturing processes, and LNP formulation as BNT162b2. Its active

substance is a modified version of the mRNA segment used in BNT162b2 encoding the spike protein of SARS-CoV-2.

2.2. Background

SARS-CoV-2, a novel β-coronavirus, is a highly transmissible and pathogenic respiratory virus responsible for the ongoing COVID-19 pandemic. Studies of SARS-CoV-2 and SARS-CoV, a closely related coronavirus that caused the 2003 SARS pandemic, demonstrated that effective antibody protection could be achieved through spike-specific antibodies.[15,16] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy of the COVID-19 pandemic. However, waning effectiveness of the authorized vaccines has been shown to occur over time and is due to the emergence of VOCs.

A large study conducted in 10 states within the US noted waning mRNA vaccine effectiveness against emergency room and urgent care encounters as well as hospitalizations, when comparing 2 months versus ≥4 months after receipt of a third dose. During the Omicron period, VE against emergency room or urgent care visits was 87% during the first 2 months after a third dose and decreased to 66% among those vaccinated 4 to 5 months earlier; VE against hospitalizations was 91% during the first 2 months following a third dose and decreased to 78% ≥4 months after a third dose.[13] In another large study conducted in approximately 2.5 million UK adults vaccinated with either ChAdOx1, BNT162b2, or mRNA-1273, approximately 80% of the participants with SARS-CoV-2 had Omicron variant infections and approximately 20% had Delta variant infections. In those who received 3 doses of BNT162b2, VE increased to 67.2% at 2 to 4 weeks before declining to 45.7% at 10 or more weeks.[14]

A recent laboratory study in Israel compared the neutralization of Omicron-infected cells in serum samples obtained from participants who had received 2 doses of BNT162b2 with neutralization in samples obtained from participants who had received 3 doses of BNT162b2. The neutralization efficiency of BNT162b2 was also tested against wild-type SARS-CoV-2 and the Beta, Delta, and Omicron variants. The importance of a third vaccine dose was evidenced by a higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose compared to the second dose. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.[17]

BNT162b5 encodes an enhanced version of the original SARS-CoV-2 spike protein mRNA that has been shown to exhibit increased thermostability of the prefusion conformation and improved immunogenicity compared to BNT162b2. Immunization of naïve mice by this version of the mRNA formulated in LNP elicited higher neutralization titers toward the ancestral strain and VOCs (Beta, Delta, and Omicron) than BNT162b2. The addition of a booster dose with an enhanced bivalent vaccine targeting the ancestral strain and Omicron variant may improve protection against SARS-CoV-2 infection, particularly against the currently dominant VOCs.

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.[18] The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age, healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. The study consists of 2 parts: Phase 1: to identify the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg [for BNT162b1]); Phase 2/3: an expanded-cohort and efficacy part to evaluate the selected vaccine candidate (BNT162b2).

The immunogenicity data from Phase 1 participants showed that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response. BNT162b2 was selected from the Phase 1 part of the study based on the overall safety, tolerability, and immunogenicity. In a mid–November 2020 analysis of 36,621 participants randomized 1:1 to vaccine or placebo and who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination schedule, the efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the active vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.[19]

In a subsequent analysis of 927 confirmed symptomatic cases of COVID-19, an efficacy rate of 91.3% was observed for BNT162b2 in preventing such cases occurring between 7 days to 6 months after the second dose.[20] Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

- 100% in preventing severe disease as defined by the CDC.
- 95.3% in preventing severe disease as defined by the FDA.
- 100% in preventing COVID-19 cases in South Africa, where the B.1.351 lineage is prevalent.

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled

through the 14 November 2020 data cutoff (N = 43,252), which includes late enrollment of additional adolescent and adult participants, were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.[19]

A booster dose (Dose 3) of BNT162b2 was administered to 306 Phase 3 participants without prior evidence of SARS-CoV-2 infection ~6 months after completing the 2-dose schedule. The immune response 1 month after administration of Dose 3 was noninferior to that observed 1 month after Dose 2 in the same participants. Furthermore, from the same analysis, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3, a high proportion of participants (99.5%) had a seroresponse at 1 month after Dose 3 compared with 98.0% at 1 month after Dose 2.[7]

On 22 September 2021, based on safety and immunogenicity data from approximately 300 immunocompetent adult booster dose recipients from Study C4591001, the FDA issued the EUA for a single booster dose of BNT162b2 30 µg for 1) individuals 65 years of age and older; 2) individuals 18 through 64 years of age at high risk of severe COVID-19; and 3) individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.[21] On 19 November 2021, the FDA amended the EUA, authorizing use of a single booster dose for all individuals 18 years of age and older after completion of primary vaccination with an FDA-approved COVID-19 vaccine.[22] On 09 December 2021, the FDA again amended the EUA to authorize the use of a single booster dose for administration to individuals 16 and 17 years of age at least 6 months after completion of primary vaccination with BNT162b2.[3] In addition, a booster dose of the vaccine is authorized in the EU and other countries, with recommendations for populations varying based on local health authority guidance.[4,5]

The per-protocol interim safety and efficacy analysis was conducted in October 2021 for Study C4591031 Substudy A. In this study, approximately 10,000 participants who had previously received 2 doses of BNT162b2 as a primary series in Study C4591001 were randomized 1:1 in Study C4591031 to receive either a 30-µg booster dose (the same dosage strength as in the 2-dose primary series) or placebo. The time between the second dose and administration of the booster dose or placebo for most participants was ≥10 to <12 months.

Symptomatic COVID-19 occurrence was measured from ≥7 days after booster or placebo, with a median follow-up of 2.5 months. During the blinded placebo-controlled study period up to a data cutoff date of 05 October 2021, there were a total of 6 cases of COVID-19 in the booster group and 123 cases in the nonboosted placebo group, in the evaluable efficacy population without evidence of prior SARS-CoV-2 infection. The observed relative VE was 95.3% (2-sided 95% CI: 89.5%, 98.3%), which reflects the reduction in disease occurrence in the boosted group versus the nonboosted group. The AE profile was generally consistent with other previously submitted clinical safety data for the vaccine, with no new safety concerns identified. No cases of myocarditis or pericarditis were reported.[23]

C4591031 Substudy E is an ongoing Phase 3 trial in approximately 2900 participants 18 years of age and older who have previously received 3 doses of BNT162b2 (30-µg dose). Participants in this substudy received a fourth dose of either BNT162b2 or BNT162b2 OMICRON (BA.1 sublineage) or a combination of both at a total dose level of either 30 µg or 60 µg. The study remains blinded at the time of this protocol, and therefore results are not yet available; however, no significant safety concerns have been identified to date.

BNT162b5 Bivalent (WT/OMI BA.2) has not been administered to humans before; however, it is highly similar to the combination vaccine under study in C4591031 Substudy E. Therefore, this study will be performed as a Phase 2 study focusing on the humoral immune response and safety of this vaccine.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with several SARS-CoV-2 vaccines now in use under marketing authorizations or EUAs. The available safety and immunogenicity data from ongoing Pfizer-BioNTech clinical trials and real-world effectiveness and safety data, combined with available nonclinical data with BNT162 vaccines and data from nonclinical and clinical trials with the same or related RNA components or antigens, support a favorable benefit/risk profile and support continued clinical development of the BNT162 family of vaccines.

Continued clinical investigation is justified, given:

- The threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection.
- The threat posed by the SARS-CoV-2 variants emerging worldwide.
- The potential need for enhancing immune responses to overcome waning immunity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the study interventions may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 Bivalent (WT/OMI BA.1) and BNT162b5 Bivalent (WT/OMI BA.2) RNA-based COVID-19 vaccine candidates		
For BNT162b2: Key identified risks for BNT162b2 include local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic reactions, such as fever, fatigue, headache, chills, muscle pain, and joint pain. Other key risks identified for BNT162b2 are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis. For BNT162b2 OMICRON (BA.1 sublineage): This vaccine has the same modRNA platform (with sequence changes limited to those that are Omicron-specific) and LNP formulation as BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2. For BNT162b5 and BNT162b5 OMICRON (BA.2 sublineage): This vaccine has the same modRNA platform (with sequence changes intended to enhance the immune response [BNT162b5] and that are Omicron-specific [BNT162b5 OMICRON (BA.2 sublineage]) and LNP formulations as BNT162b2; therefore, the safety profile is expected to be similar.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. Data available from the C4591001 study showed low incidence of severe or serious events and no clinically concerning safety observations across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[19] Anaphylaxis: Frequency not known. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients. Postauthorization safety data surveillance has confirmed the safety profile observed in Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	Local reactions and systemic events will be recorded using a reactogenicity e-diary to monitor local reactions and systemic events in real time. Collection of AEs from signing of the ICD through 1 month and SAEs through 6 months after study vaccination. DMC review throughout the study to review all safety data. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.10.8.

Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Monitoring for cases of COVID-19 developing during the study as part of the COVID-19 surveillance.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in the study may be:

- Receipt of a further dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey better protection against the SARS-CoV-2 wild-type (ancestral) strain and VOCs during a global pandemic.
- Access to COVID-19 diagnostic testing.
- Contributing to research to help others in a time of global pandemic.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants as stated in Section 2.3.1, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccines are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Estimands	Endpoints
Primary Safety		
To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Primary Immunogenicity		
To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)-neutralizing titers • SARS-CoV-2 Omicron (BA.1)-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
Exploratory		
To describe the immune response to emerging VOCs		• SARS-CoV-2 neutralizing titers for Omicron sublineages and VOCs not already specified

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

4. STUDY DESIGN

4.1. Overall Design

For the purposes of this protocol, study intervention refers to:

- BNT162b5 Bivalent (WT/OMI BA.2)
- BNT162b2 Bivalent (WT/OMI BA.1)

This study is a randomized, active-controlled, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a new bivalent vaccine at the 30-µg dose level. The study duration for each participant will be approximately 6 months. Refer to the schema in Section 1.2.

Participants will be randomized at a ratio of 1:1 to receive a single dose of 1 of the 2 study interventions. Participants will be stratified by the number of months since the last dose of COVID-19 vaccine received prior to entering the study (3-6 months or >6 months). Approximately 200 participants will be enrolled in the study.

Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed and study visits or other procedures may be discontinued.

An EDMC will review cumulative unblinded data throughout the study. Refer to Appendix 1, Section 10.1.5.1.

4.2. Scientific Rationale for Study Design

The immune response following vaccination with BNT162b2 has been observed to wane with time, and a booster dose of BNT162b2 has demonstrated improvement in immune response, albeit to a lesser degree against some variants, particularly Omicron, of the original SARS-CoV-2 virus. This is the first clinical study of BNT162b5 Bivalent aimed to improve the current protection elicited by BNT162b2. Because of the similarity with the combination and bivalent vaccines currently being studied in C4591031 Substudy E (BNT162b2 Wild Type and BNT162b2 OMICRON [sublineage BA.1]) and because there have been no safety concerns to date with that vaccine, this is a Phase 2 study. As COVID-19 surveillance is conducted in C4591031 Substudy E, in this small FIH study, a confirmed COVID-19 diagnosis will be considered an AESI.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), in the age group of the study, to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

Given the relatively small size of the study, there may be less representation with respect to race, ethnicity, and geographic location.

4.2.2. Choice of Contraception/Barrier Requirements

BNT162b2 is approved for use without any contraceptive precautions. BNT162b5 Bivalent (WT/OMI BA.2) is also an RNA-LNP vaccine utilizing modRNA. There is no suspicion of human teratogenicity based on the intended pharmacology. See Appendix 4 for contraception requirements.

4.3. Justification for Dose

Based on data from the Phase 1 component of clinical trial C4591001 and available nonclinical data, the modRNA BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2/3 evaluation of safety, immunogenicity, and efficacy after 2 doses administered 3 weeks apart and is the authorized dose level for the third dose administered at least 5 months following the second dose. The 30-µg dose level of BNT162b2 was shown to be effective and has been approved in multiple countries worldwide for the primary 2-dose series as well as for third and fourth (booster) doses.

4.4. End of Study Definition

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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. Participants 18 through 55 years of age at randomization.

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

Participant and Disease Characteristics:

2. Participants willing and able to comply with all scheduled visits/contacts, investigational plan, laboratory tests, 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. Participant is capable of giving signed informed consent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusion Criteria:

5. Participants who have received 1 booster dose of a US-authorized COVID-19 vaccine, with the last prior dose being 90 or more days before Visit 1 (Day 1).

   Note: Documented confirmation of prior COVID-19 vaccines received must be obtained prior to randomization. All prior COVID-19 vaccines must be authorized for use in the US.

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

5. 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.

Prior/Concomitant Therapy:

6. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment through conclusion of the study.

Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease) or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

Prior/Concurrent Clinical Study Experience:

8. Participation in other studies involving a study intervention within 28 days before randomization. Anticipated participation in other studies within 28 days after receipt of study intervention in this study.

Other Exclusion Criteria:

9. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant 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 acceptable 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, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, 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 enrolled in the study. 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, and any SAEs.

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/Administration of Study Intervention

The following conditions may allow a participant to receive study intervention once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

1. A positive SARS-CoV-2 test result (NAAT or rapid antigen test) within the previous 28 days.

2. Current febrile illness (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration. This includes symptoms that could represent a potential COVID-19 illness (refer to Section 8.4.8).

3. Note: The participant should be directed to seek additional testing through his/her primary healthcare provider at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

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

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

6. 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(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to:

- BNT162b5 Bivalent (WT/OMI BA.2) =

  BNT162b5 Wild Type* and BNT162b5 OMICRON (B.1.1.529) sublineage BA.2

  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)

- BNT162b2 Bivalent (WT/OMI BA.1) =

  BNT162b2 Wild Type* and BNT162b2 OMICRON (B.1.1.529) sublineage BA.1

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

*Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Study Interventions Administered

Study Interventions		
Intervention Name	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2]) Preformulated as a single vial (no dilution required)	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Type	Vaccine	Vaccine
Dose Formulation	Multidose vial[a]	Multidose vial[a]
Unit Dose Strength(s)	100 µg/mL	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b5 Wild Type and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])
Route of Administration	Intramuscular injection	Intramuscular injection

Study Interventions		
Use	Experimental	Experimental and active comparator
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vial will be labeled as required per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Vial will be labeled as required per country requirement.

a. Study intervention will be administered as a single dose from multidose vials.

Study Arms		
Arm Title	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Arm Type	Experimental	Experimental and active comparator
Arm Description	Participants will receive 30 µg of BNT162b5 Bivalent (WT/OMI BA.2) at Visit 1.	Participants will receive 30 µg of BNT162b2 Bivalent (WT/OMI BA.1) at Visit 1.
Associated Intervention Labels	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])

6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 1 in accordance with the study's SoA (Section 1.3).

Study intervention should be administered intramuscularly by injecting 0.3 mL of vaccine into the deltoid muscle, preferably of the nondominant arm.

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, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) 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, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM for storage conditions of the study intervention once prepared.

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff 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 IPM. 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 IPM.

6.2.1. Preparation and Dispensing

See the IPM 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 will be prepared by qualified unblinded site personnel according to the IPM. The study intervention will be administered by unblinded study staff to blinded participants.

Study intervention will be provided in multidose vials; however, they are intended for single use, as outlined in the IPM.

6.3. Assignment to Study Intervention

Allocation of participants to vaccine groups will proceed through the use of an IRT system. 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 randomization number corresponding to the assigned vaccine group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Participants will be stratified by the number of months since the last dose of the COVID-19 vaccine received prior to entering the study (3-6 months or >6 months).

Study intervention will be dispensed at the study visits summarized in the SoA.

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

6.4. Blinding

This study will be observer-blind at the site level with respect to study intervention allocation and open-label to most Pfizer staff. Refer to Section 6.4.3.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

In this observer-blind 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 there are differences in physical appearance of the study interventions, the study intervention will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The study will be unblinded to site personnel at a time decided by Pfizer.

6.4.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, the majority of Pfizer staff will be unblinded to study intervention allocation. All laboratory testing personnel will remain blinded to study intervention assigned/received throughout the study.

6.4.4. 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 vaccine 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 study medical monitor 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 IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the unblinded 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 ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.6. Dose Modification

Not applicable to this study.

6.7. Continued Access to Study Intervention After the End of the Study

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

6.8. 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 study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

6.9. Prior and Concomitant Therapy

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

- Prohibited medications listed in Section 6.9.1 will be recorded in the concomitant medication CRF.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.

- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.

6.9.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per Section 7.2). 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. With the exception of seasonal and pandemic influenza vaccine that 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 through 28 days after administration of study intervention.

- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration through conclusion of the study.

- Receipt of any other (nonstudy) coronavirus vaccine at any time during study participation.

- 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.

6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 6.9.1 required for treatment of preexisting conditions or acute illness is permitted.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. The participant will be permanently discontinued from the study at that time. Reasons for discontinuation from the study include the following:

- Lost to follow-up;
- Death;
- Study terminated by Pfizer;
- AEs;
- Participant request;
- Investigator request;
- Select protocol deviations (Note: receipt of a COVID-19 vaccine outside of the study will result in study withdrawal).

If a participant withdraws from the study, they 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 Pfizer 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 will be performed and no additional data will be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

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 study procedures and/or postvaccination 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 the participant 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 return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline 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 date of birth will be collected to critically evaluate the immune response and safety profile by age.

A participant number will be assigned.

A randomization number and study intervention allocation will be obtained from the IRT system.

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

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 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 they have 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.

Safety and laboratory results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 160 mL. 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 56 consecutive days.

8.1.1. Baseline Procedures

The baseline procedures (not detailed in subsequent sections) are listed below. They are performed at Visit 1 (Day 1):

- Record demography data (including date of birth, sex, race, and ethnicity).
- Record any medical history of clinical significance.
- Measure and record height and weight.

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Vaccine-Induced Immunogenicity

Blood samples will be obtained at each visit for immunogenicity testing at the central laboratory. The following assays will be performed on serum samples at each visit:

- SARS-CoV-2 neutralization assay (reference strain)
- SARS-CoV-2 neutralization assays (Omicron BA.1, Omicron BA.2; other VOCs of interest, including other Omicron sublineages, may also be evaluated)

8.2.2. N-Binding Antibody Test

The N-binding antibody test will be performed by the central laboratory on each blood sample to establish prior exposure to SARS-CoV-2 up to each time point. These data will be used for study analyses.

8.2.3. 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 analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. 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 vaccines under study in this protocol, to inform the development of other vaccines or vaccine-related 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 their 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.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

A complete physical examination will include 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.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

The participant's body temperature will be measured at Visit 1, prior to study vaccination.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.3.4. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days from the day of 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. Generally, these data do not need to be reported by the investigator in the CRF as AEs. However, if a participant withdraws because of events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals to evaluate participant compliance and 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.

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[24]

8.3.4.2. Local Reactions

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

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

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify Pfizer. A Grade 4 reaction will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the case report form.

8.3.4.3. Systemic Events

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

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify Pfizer. A Grade 4 systemic event will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 2. Systemic Event Grading Scale

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

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if the test result is positive, the symptoms should be recorded as an AE of COVID-19 rather than as systemic events in the reactogenicity e-diary. Such COVID-19 diagnoses should be reported as AEs as per Section 8.4. AEs of confirmed COVID-19 are considered to be AESIs (refer to Section 8.4.8).

8.3.4.4. 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. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 3 during analysis.

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 Pfizer. Fevers >40.0°C (>104.0°F) will be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (Section 10.3.3).

Table 3. Scale for Fever

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

8.3.4.5. Antipyretic/Analgesic Medication

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

8.3.5. 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 Visit 1, before the administration of the study intervention 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 not be administered the study intervention dose and will be withdrawn from the study.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 (see Section 7.1).

During the active collection period as described in Section 8.4.1, 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.

8.4.1. 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 3 (approximately 1 month after the participant's study vaccination).

In addition, any AE occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent through Visit 5 (approximately 6 months after the participant's study vaccination).

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues 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 permanently discontinues or temporarily discontinues the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek information on 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 they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Reporting 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 its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward 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.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting 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 28 days after the study intervention. Beyond 28 days after the study intervention, any pregnancy that occurs will not be considered EDP for this study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting 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 should be reported as an SAE;

- 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding within 28 days after receiving the study intervention.

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

The following events are considered AESIs:

- Confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination. See Section 8.10.8.

- Confirmed COVID-19 diagnosis through end of the study (clinical signs/symptoms and positive SARS-CoV-2 NAAT or rapid antigen test).

The current list of symptoms according to the CDC can be found at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.

Should the participant receive a positive SARS-CoV-2 test (NAAT or rapid antigen) result that is not accompanied by symptoms, details of the positive test should be recorded on the designated CRF (not the AE CRF).

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Vaccination Errors

Vaccination 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.

Vaccination errors are recorded and reported as follows:

Recorded on the Vaccination Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the vaccination error	Only if associated with an SAE

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination 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 vaccination errors occurring to a study participant are to be captured on the vaccination error page of the CRF, which is a specific version of the AE page.

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.

8.9. Health Economics

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

8.10. Study Procedures

8.10.1. Visit 1 – Study Intervention Administration – 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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day. Ensure that procedures listed

prior to administration of the vaccine are conducted prior to vaccination and on the day of the vaccination.

- Assign a participant number using the IRT system. If participant is from a prior Pfizer COVID-19 study, record the participant number of the prior study in the CRF.
- 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 medical history, including confirmed COVID-19 diagnosis (see Section 8.4.8) or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test), and any other medical history of clinical significance.
- Review documentation of all prior COVID-19 vaccinations. All vaccines must be authorized for use in the US.
- Perform urine pregnancy test on WOCBP as described in Section 8.3.5.
- Discuss contraceptive use as described in Section 5.3.1.
- Measure the participant's height and weight.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination (refer to Section 8.3.1), and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and before vaccination, measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and before vaccination, obtain a nasal (midturbinate) swab (collected by site staff).
- On the day of and before vaccination, collect a blood sample (approximately 50 mL) for testing of immunogenicity and N-binding antibody.

- Blinded site staff will obtain the participant's randomization number and vaccine vial allocation using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle, preferably of the nondominant arm. Please refer to the IPM 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.

- Record AEs as described in Section 8.4.

- Explain the e-diary technologies available for this study (see Section 8.3.4) 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 through Day 7, with Day 1 being the day of vaccination (see Section 8.3.4.1 through Section 8.3.4.5).

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

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.8).

- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary device 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.

8.10.2. Visit 2 – 1-Week Follow-Up Visit (6 to 8 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Discuss contraceptive use as described in Section 5.3.1.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day the reactogenicity e-diary was completed.
- If the 7-day e-diary period has ended: Collect the participant's e-diary provisioned device or assist the participant to remove the study application from his or her own personal device.
- If the 7-day reactogenicity period is ongoing: Remind the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 through 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.
- Remind 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.8).
- Schedule an appointment for the participant to return for the next study visit.
- If the 7-day reactogenicity period is ongoing: 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.

8.10.3. Visit 3 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Confirm contraceptive use as described in Section 5.3.1.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.

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

- Collect the participant's e-diary provisioned device or assist the participant to remove the study application from his or her own personal device.

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

- 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.

8.10.4. Visit 4 – 3-Month Follow-Up Visit (84 to 98 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.

- Record nonstudy vaccinations as described in Section 6.9.

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.

- Record AEs as described in Section 8.4.

- Collect a blood sample (approximately 20 mL) for immunogenicity testing, unless advised otherwise by Pfizer.

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

- 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.

8.10.5. Visit 5 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing, unless advised otherwise by Pfizer.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

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

If a Grade 3 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) 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 a suspected Grade 4 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) 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 that it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

8.10.7. SARS-CoV-2 NAAT Results

- A nasal (midturbinate) swab for SARS-CoV-2 NAAT is obtained at the vaccination visit (Visit 1/Day 1).

Research laboratory–generated positive results from the vaccination visit swabs will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare provider at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

8.10.8. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after the study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis. In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the 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. Statistical Hypothesis

There is no formal hypothesis testing. All statistical analyses will be descriptive.

9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in Section 3.

The primary safety objective evaluations are based on the safety population. In general, completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially missed reactogenicity e-diary data (eg, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days. Missing AE start 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 the evaluable immunogenicity population (Section 9.2). 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.

9.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed for the study as there is no statistical hypothesis.

9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.

Population	Description
All-available immunogenicity (mITT)	All randomized participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

9.3.1. General Considerations

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population 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.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson). The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.

9.3.1.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

9.3.1.3. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

9.3.1.4. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points. GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.5. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

9.3.2. Primary Endpoints/Estimands Analysis

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group.

Endpoint	Statistical Analysis Methods
Immunogenicity	For each primary immunogenicity estimand described in Section 9.3.1, • GMTs and 2-sided 95% CIs will be provided for each vaccine group at each time point for SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)-neutralizing and reference-strain–neutralizing titers. GMTs will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.3. • GMFRs of SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)-neutralizing and reference-strain–neutralizing titers from baseline (pre–Dose 1) to each subsequent time point, along with the associated 2-sided 95% CIs will be provided for each vaccine group. GMFRs will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.4. • The percentages of participants with seroresponse to Omicron (sublineages BA.1 and BA.2)- and reference-strain–neutralizing titers at each time point after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. The percentages of participants with seroresponse will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. • GMTs, GMFRs, and percentages of participants with seroresponse, along with the associated 95% CIs, will also be summarized by baseline SARS-CoV-2 infection status.

9.3.3. Exploratory Endpoints

Endpoint	Statistical Analysis Methods
Immune response to emerging VOCs	• GMTs of SARS-CoV-2 VOC-neutralizing titers for Omicron sublineages and VOCs not already specified, along with the associated 2-sided 95% CIs, will be provided at specific time points for each vaccine group. GMFRs from baseline (pre–Dose 1) to each subsequent time point, percentage of participants with seroresponse at each time point after vaccination, along with the associated 2-sided 95% CIs, may also be provided for each vaccine group.

9.4. Interim Analyses

As this is a sponsor open-label Phase 2 study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

9.4.1. Analysis Timing

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

- Safety and immunogenicity data through Visit 3 (1 month after study vaccination).
- Safety and immunogenicity data through Visit 5 (6 months after study vaccination).

Additional analyses may be conducted if required for regulatory purposes.

9.5. Sample Size Determination

The sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

For safety outcomes, Table 4 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 2%, with 100 participants in a vaccine group, there is 87% probability of observing at least 1 AE.

Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates

Assumed True Event Rate of an AE	N=100
0.1%	0.10
0.5%	0.39
1%	0.63
2%	0.87
3%	0.95
4%	0.98
5%	0.99

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, 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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide Pfizer with sufficient, accurate financial information as requested to allow Pfizer to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, 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, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each 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 their 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 their 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 their right to access and correct their personal data and to withdraw consent for the processing of their 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 on which 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 IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.4. 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an EDMC. The EDMC is independent of the study team and includes only external members. The EDMC charter describes the role of the EDMC in more detail.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will

communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

10.1.6. 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/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-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 data from these trials available

24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor's designee.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. 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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 the ICH 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.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff

are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

If appropriate, a pregnancy test will be performed at times defined in the SoA.

- Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for participants who are WOCBP.

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.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
• New condition 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 or 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 that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting 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	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.
** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or 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 or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or 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 or SAE.

Assessment of Intensity

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.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting 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 submitted documents.
- 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 an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier 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 as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 agrees to use an acceptable contraceptive method 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 a 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.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she 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.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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 WOCBP 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.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.

Sexual Abstinence

8. 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.

Other Effective Methods

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 "adaptors" 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 T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 Pfizer.

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 T bili for suspected Hy's law cases, 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, or 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, 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 T bili 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: Kidney Safety Monitoring Guidelines

10.6.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.6.2. Age-Specific Kidney Function Calculation Recommendations

10.6.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	Scr (*mg/dL*)	Scys (*mg/L*)	Recommended eGFR Equation
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr (*mg/dL*)**	**Scys (*mg/L*)**	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

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10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE/KDIGO criteria.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BNT162b2 Bivalent (WT/OMI BA.1)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.1)
BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529 sublineage BA.2)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
e-diary	electronic diary
EDB	exposure during breastfeeding
EDMC	external data monitoring committee
EDP	exposure during pregnancy

Abbreviation	Term
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
EU	European Union
EUA	emergency use authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
N/A	not applicable
N-binding	SARS-CoV-2 nucleoprotein–binding
NAAT	nucleic acid amplification test

Abbreviation	Term
NIMP	noninvestigational medicinal product
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
P6' S	SARS-CoV-2 full-length, P6 prime mutant, prefusion spike glycoprotein
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
RNA	ribonucleic acid
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
Th1	T-helper type 1
UK	United Kingdom
ULN	upper limit of normal
US	United States
VE	vaccine efficacy
VOC	variant of concern
WOCBP	woman/women of childbearing potential

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Document Approval Record

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Document Title:	AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2 OBSERVER-BLIND STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BIVALENT BNT162b RNA-BASED VACCINE CANDIDATE AS A BOOSTER DOSE IN COVID-19 VACCINE–EXPERIENCED HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
[redacted]	14-Jun-2022 14:34:21	Business Line Approver
[redacted]	14-Jun-2022 17:53:56	Final Approval

AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2/3 STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BIVALENT BNT162b RNA-BASED VACCINE CANDIDATES AS A BOOSTER DOSE IN COVID-19 VACCINE–EXPERIENCED HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted by:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT/CTIS Number:	2022-002008-19
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	EMEA-002861-PIP02-20-M03
Protocol Number:	C4591044
Phase:	2/3

Brief Title:
A Study to Learn About New COVID-19 RNA Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals

Document History

Document	Version Date
Original protocol	14 June 2022
Amendment 1	27 July 2022
Amendment 2	24 August 2022

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

Amendment 2 (24 August 2022)

Overall Rationale for the Amendment:

Inclusion of a third cohort to allow for a sufficiently powered evaluation of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose in BNT162b2-experienced participants ≥18 years of age. Added corresponding objectives, estimands, and endpoints and details in the statistical methods sections. Study intervention details and background information supporting inclusion of this cohort were added.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Cover page	Amended the title to remove blinding level and to change from Phase 2 to Phase 2/3. Corrected Study Intervention Name to reflect 'BNT162b'.	With addition of Cohort 3, the mix of blinding levels by cohort is detailed in Sections 4.1 and 6.4.	Substantial
Section 4.2 Scientific Rationale for Study Design	Update to include Phase 3 per title change.	Cohort 3 is considered a Phase 3 study, consistent with how we have described prior variant vaccine evaluations in 300 participants per group.	
Section 1.1 Synopsis	Updated rationale on prevalence of Omicron BA.4 and BA.5 sublineages.	To reflect the evolving pandemic and medical need for prevention of Omicron BA.4 and BA.5 sublineages.	Substantial
Section 1.1 Synopsis	Updated text with respect to the addition of Cohort 3, including the protocol title.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 1.2 Schema	Added Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3 Schedule of Activities	Noted that PBMC sampling and HLA typing are not applicable for Cohort 3. Added blood sample collection in the potential COVID-19 illness visit for participants who have this visit in person.	Cohort 3 is not part of the PBMC subset. To comply with regulatory agency requests.	Substantial
Section 2 Introduction	Updated text on the prevalence of Omicron BA.4 and BA.5 sublineages.	To reflect the evolving pandemic and medical need for prevention of Omicron BA.4 and BA.5 sublineages.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated to reflect the addition of Cohort 3. For the Cohort 2 primary immunogenicity objective, added clarification to the selection of comparator participants from C4591031 Substudy E.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5). To comply with regulatory agency requests.	Substantial
Section 4.1 Overall Design	Updated to reflect the addition of Cohort 3. For the Cohort 2 primary immunogenicity objective, added clarification to the selection of comparator participants from C4591031 Substudy E.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5). To comply with regulatory agency requests.	Substantial
Section 5.1 Inclusion Criteria	Updated to reflect the addition of Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 6 Study Interventions	Updated to reflect the addition of Cohort 3.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 8.1 Administrative and Baseline Procedures	Clarifications made to blood volumes and added blood sample for in-person potential COVID-19 illness visits.	To comply with regulatory agency requests and clarify volume calculations.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 8.10.8 Potential COVID-19 Illness Visit	Added blood sample collection in the potential COVID-19 illness visit for participants who have this visit in person.	To comply with regulatory agency requests.	Substantial
Section 9 Statistical Considerations	Updated to reflect the addition of Cohort 3 and its associated analyses.	To obtain additional data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 5.2 Exclusion Criteria	Clarifications.	In response to site inquiries and for alignment with other C459 studies.	Nonsubstantial
Section 6 Study Interventions and Concomitant Therapy	Added: "For the purposes of this protocol, study intervention refers to investigational product"	Content was added to match current protocol template.	Nonsubstantial
Section 6.9.1 Prohibited During the Study	Clarifications.	In response to site inquiries and for alignment with other C459 studies.	Nonsubstantial
Section 8.2.1 Surveillance for COVID-19	Title of section updated.	Title updated to better reflect objective.	Nonsubstantial
Section 8.3.4.3 Systemic Events	Corrected instructions explaining what should occur in the event of a local positive SARS-CoV-2 test in a symptomatic participant.	To align with sections 8.4.8, 8.10.7 and 8.10.8.	Nonsubstantial
Section 8.3.4.4 Fever	Edits made to Table 6: Scale for Fever.	To align how Celsius temperature ranges were presented with FDA reference and content within section.	Nonsubstantial
Section 8.4.5.1 Exposure During Pregnancy	Updated to reflect study definition of Exposure During Pregnancy as per other content within section.	Updated to maintain consistency within section.	Nonsubstantial
All	Minor editorial changes.	Corrections or minor edits in line with amendment updates.	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Interventional, Randomized, Active-Controlled, Phase 2/3 Study to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals

Brief Title:

A Study to Learn About New COVID-19 RNA Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals

Regulatory Agency Identification Numbers:

US IND Number:	19736
EudraCT/CTIS Number:	2022-002008-19
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	EMEA-002861-PIP02-20-M03
Protocol Number:	C4591044
Phase:	2/3

Rationale:

BNT162b2 (Comirnaty®) is an RNA-based vaccine that, as of April 2022, has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 140 countries for the prevention of COVID-19 caused by SARS-CoV-2. The vaccine encodes the spike protein with a modRNA, is encapsulated in RNA-LNPs, and has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials, as well as in real-world usage. Since the start of the pandemic, several VOCs have emerged, causing surges in infection rates, despite uptake of vaccines. Currently, the SARS-CoV-2 Omicron variant B.1.1.529 and its sublineages are dominant in many countries and, within the US, the BA.4 and BA.5 sublineages were responsible for 94.1% of all sequenced COVID-19 cases as of the week ending 13 August 2022. The BA.4 and BA.5 sublineages demonstrate substantial immune escape from neutralizing antibodies induced by both infection and immunization, which has been attributed to the L452R and F486V spike mutations within the protein sequence of BA.4 and BA.5. Moreover, studies have demonstrated that the effectiveness of BNT162b2 against SARS-CoV-2 infection and COVID-19 wanes over a period of months, particularly in the context of VOCs.

In light of the waning effectiveness of the primary 2-dose series of BNT162b2 as well as the existence of VOCs with cumulative mutations in the spike protein that are resilient to the existing immune response, particularly Omicron, development of an enhanced bivalent vaccine that could generate an improved immune response, including against VOCs, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate the following vaccine candidates:

BNT162b5 Bivalent (WT/OMI BA.2): an enhanced BNT162b RNA-based vaccine, consisting of a modified version of the SARS-CoV-2 spike protein mRNA, targeting the ancestral strain of the virus, in combination with mRNA encoding the spike protein of the Omicron variant (BA.2 sublineage).

BNT162b2 Bivalent (WT/OMI BA.4/BA.5): consisting of the original SARS-CoV-2 spike protein mRNA, targeting the ancestral strain of the virus, in combination with mRNA encoding the spike protein of the Omicron variant (BA.4/BA.5 sublineage).

Objectives, Endpoints, and Estimands:

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Objectives	Estimands	Endpoints
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFRs from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers

Objectives	Estimands	Endpoints
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[d] or 60 µg[d] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55[d], and >55[d] years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[b]–neutralizing titers

Objectives	Estimands	Endpoints
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers SARS-CoV-2 reference-strain[b]–neutralizing titers
Exploratory		
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine group and age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[e] and at the convalescent visit.		• SARS-Cov-2–neutralizing titers previously specified for the respective cohorts
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to emerging VOCs.		• SARS-CoV-2–neutralizing titers for VOCs not already specified

Objectives	Estimands	Endpoints
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[b] and Omicron variant in a subset of participants with PBMC samples collected.		

a. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. Reference strain is also referred to as the Wild Type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
c. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
d. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received Bivalent BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be randomly selected for this objective. The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.
e. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

Overall Design:

This study is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent vaccines. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan.

Cohort 1: Participants 18 through 55 years of age will be randomized at a ratio of 1:1 to receive a single 30-µg dose of either BNT162b5 Bivalent (WT/OMI BA.2) or BNT162b2 Bivalent (WT/OMI BA.1) as a second booster dose. Participants will be stratified by the number of months since the last dose of the COVID-19 vaccine received prior to randomization (3 to 6 months [90 to 180 days] or >6 months [>180 days]).

Cohort 2: Participants 12 through 17 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label). Participants 18 through 55 years of age and >55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will be randomized 1:1 within each age group to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg as a second booster dose (observer-blind).

Cohort 2: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	12-17 years	3	150-365 days	30 µg	100	Open-label
2	18-55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
3	18-55 years	3	150-365 days	60 µg	100	
4	>55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
5	>55 years	3	150-365 days	60 µg	100	

Cohort 3: Participants 18 years of age and older who have received 3 prior 30-µg doses of BNT162b2, with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label).

Cohort 3: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	18-55 years	3	150-365 days	30 µg	200	Open-label
2	>55 years	3	150-365 days	30 µg	200	Open-label

Number of Participants:

Cohort 1: Approximately 200 participants will be enrolled.

Cohort 2: Approximately 500 participants will be enrolled.

Cohort 3: Approximately 400 participants will be enrolled.

Study Population:

The inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Ages for each cohort as follows:

   Cohort 1: Participants 18 through 55 years of age at randomization.

   Cohort 2: Participants ≥12 years of age at Visit 1.

   Cohort 3: Participants ≥18 years of age at Visit 1.

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

Participant and Disease Characteristics:

2. Participants and participants' parent(s)/legal guardian(s), as appropriate, willing and able to comply with all scheduled visits/contacts, investigational plan, laboratory tests, 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 signed informed consent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

   The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian (as defined in Appendix 1, Section 10.1.3) and the participant's assent, when applicable, before any study-specific activity is performed. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

Other Inclusion Criteria:

5. Cohort 1: Participants who have received 1 booster dose of a US-authorized COVID-19 vaccine, with the last prior dose being 90 or more days before Visit 1 (Day 1).

   Note: Documented confirmation of prior COVID-19 vaccines received must be obtained prior to randomization. All prior COVID-19 vaccines must be authorized for use in the US.

   Cohort 2 and Cohort 3: Participants who have received 3 prior 30-µg doses of BNT162b2, with the last dose being 150 to 365 days before Visit 1 (Day 1).

   Note: Documented confirmation of prior doses of BNT162b2 received must be obtained prior to randomization.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

5. 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.

Prior/Concomitant Therapy:

6. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease), or radiotherapy, within 60 days before enrollment or planned receipt through conclusion of the study.

   Note: Chronic systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

Prior/Concurrent Clinical Study Experience:

8. Participation in other studies involving receipt of a study intervention within 28 days before randomization. Anticipated participation in other studies involving a study intervention from randomization through the end of this study.

Other Exclusion Criteria:

9. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Study Arms and Duration:

The study duration for each participant will be approximately 6 months. For the purposes of this protocol, study intervention refers to:

Cohort 1

- BNT162b5 Bivalent (WT/OMI BA.2) =

  BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529) sublineage BA.2

  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)
- BNT162b2 Bivalent (WT/OMI BA.1) =

  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.1

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 1		
Intervention Name	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2]) Preformulated as a single vial (no dilution required)	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1]) Preformulated as a single vial (no dilution required)
Arm Name **(group of participants receiving a specific study intervention or no study intervention)**	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Unit Dose Strength(s)	100 µg/mL	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b5 Wild Type and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental and active comparator
IMP or NIMP/AxMP	IMP	IMP

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Study Arms – Cohort 1		
Arm Title	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Arm Type	Experimental	Experimental and active comparator
Arm Description	Participants will receive 30 µg of BNT162b5 Bivalent (WT/OMI BA.2) at Visit 1.	Participants will receive 30 µg of BNT162b2 Bivalent (WT/OMI BA.1) at Visit 1.

Cohort 2

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) =
  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 2	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg or 60 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) (30 µg BNT162b2 Wild Type and 30 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020); it is also referred to in this protocol as the reference strain.

Study Arms – Cohort 2					
Arm Title	Group 1: 12-17 years, 30 µg	Group 2: 18-55 years, 30 µg	Group 3: 18-55 years, 60 µg	Group 4: >55 years, 30 µg	Group 5: >55 years, 60 µg
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg

Cohort 3

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) =
  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 3	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name **(group of participants receiving a specific study intervention or no study intervention)**	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020); it is also referred to in this protocol as the reference strain.

Study Arms – Cohort 3		
Arm Title	Group 1: 18-55 years, 30 µg	Group 2: >55 years, 30 µg
Arm Type	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1

Statistical Methods:

Cohorts 1 and 2:

For the objectives evaluated separately within Cohort 1 and Cohort 2, the sample size is not based on any statistical hypothesis testing since all objectives are descriptive. The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group. The primary immunogenicity objectives will be evaluated descriptively by GMT, GMFR, and percentage of participants with seroresponse of SARS-CoV-2–neutralizing titers at the various time points.

Cohort 2 + Cohort 3 combined:

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each age group.

For the >55-age group, the primary immunogenicity objective will be evaluated by GMR of the Omicron BA.4/BA.5–neutralizing titers and difference in percentage of participants with seroresponse to the Omicron BA.4/BA.5 strain induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to BNT162b2 at 1 month after the study vaccination. The BNT162b2 group is a historic comparator, from approximately 300 participants >55 years of age who received BNT162b2 30 µg as a fourth dose in C4591031 Substudy E expanded cohort, after 3 prior 30-µg doses of BNT162b2. Assuming a 20% nonevaluable rate, with approximately 300 participants to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in this study and approximately 300 participants who received BNT162b2 from C4591031 Substudy E, there will be approximately 480 evaluable participants (240 BNT162b2 Bivalent [WT/OMI BA.4/BA.5] and 240 BNT162b2) contributing to the immunogenicity evaluation. Superiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

For the 18- through 55-age group, the primary immunogenicity objective will be evaluated by GMR of the Omicron BA.4/BA.5–neutralizing titers and difference in percentage of participants with seroresponse to the Omicron BA.4/BA.5 strain induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in the >55-age group at 1 month after the study vaccination. Assuming a 20% nonevaluable rate, with approximately 300 participants to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in each age group, there will be approximately 480 evaluable participants (240 in the 18- through 55-age group and 240 in the >55-age group) contributing to the immunogenicity evaluation. Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

The secondary immunogenicity objective for the >55-age group will be evaluated by GMR of the reference-strain–neutralizing titers induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to BNT162b2 (historic comparator) at 1 month after the study vaccination. Noninferiority based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

The primary objective for the >55-age group will be evaluated first, followed by the secondary objective for GMR in the >55-age group and then the primary objective for the 18-through 55-age group. Each of these objectives will be evaluated only if the previous objective is met. Each primary objective involves 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error is fully controlled.

The other secondary immunogenicity objectives will be evaluated descriptively by GMT, GMFR, the difference in percentages of participants with seroresponse, and the associated 95% CIs for SARS-CoV-2–neutralizing titers at the various time points.

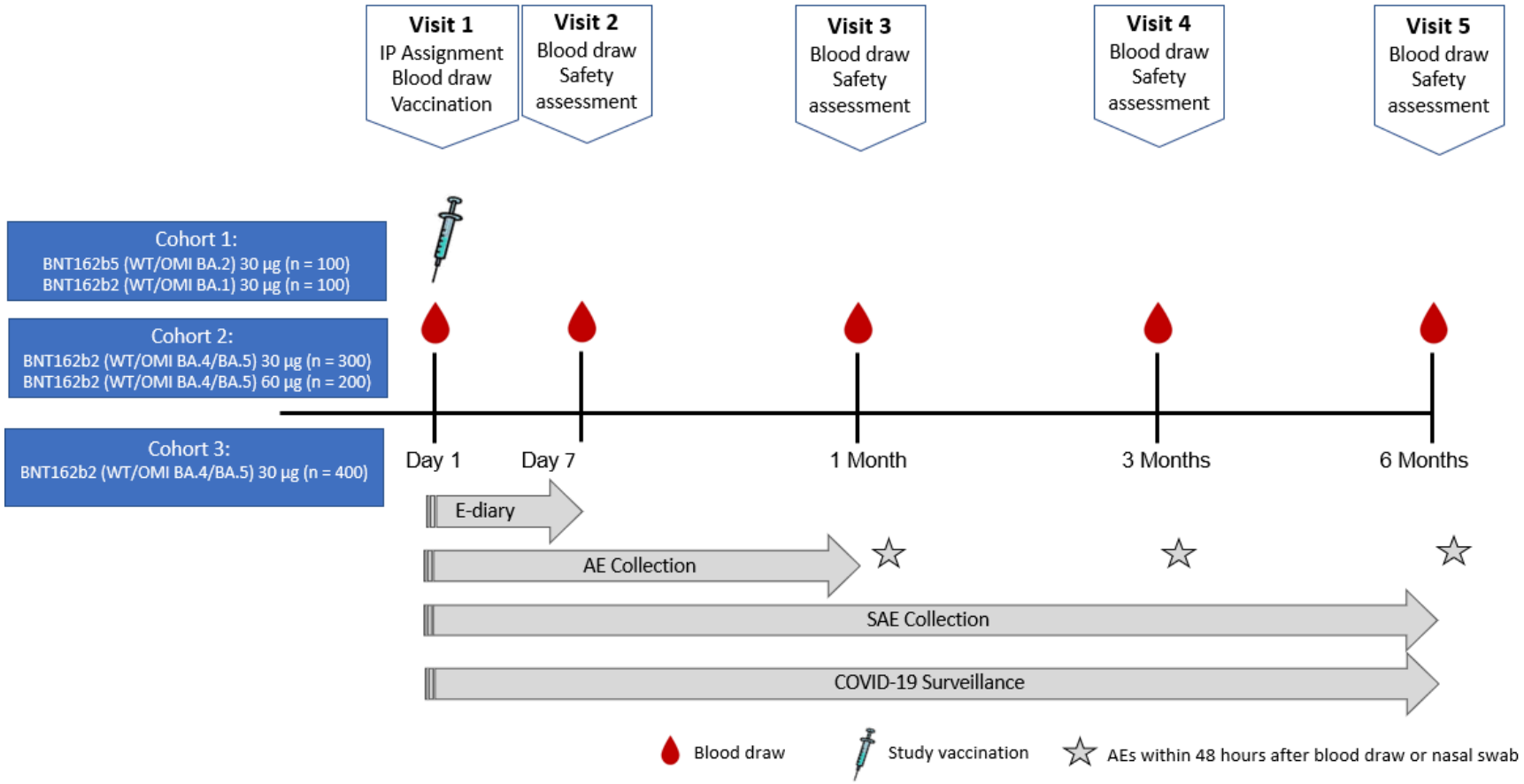
Ethical Considerations:

The available safety and immunogenicity data from ongoing Pfizer-BioNTech clinical trials and real-world effectiveness and safety data, combined with available nonclinical data with BNT162 vaccines and data from nonclinical and clinical trials with the same or related RNA components or antigens, support a favorable benefit/risk profile and support clinical development of BNT162b5 and BNT162b2 bivalent vaccines. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to healthy participants.

- As BNT162b5 Bivalent (WT/OMI BA.2), BNT162b2 Bivalent (WT/OMI BA.4/BA.5), and BNT162b2 Bivalent (WT/OMI BA.1) use the same modRNA platform and LNP formulation as BNT162b2, their safety profiles are expected to be similar to that of BNT162b2. Based on the experience with BNT162b2, the potential risks for BNT162b2 include the following:
    - Local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, muscle pain, and joint pain.
    - Very rare cases of myocarditis and pericarditis have been reported after authorization in recipients of BNT162b2.
    - Cases of anaphylaxis have been reported; however, the frequency is not estimable from the available data.

- The study procedure–related risks include:
    - Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.
    - Venipuncture will be performed during the study.
- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.

1.2. Schema



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.

An unplanned potential COVID-19/MIS-C illness visit and unplanned potential COVID-19/MIS-C convalescent visit are required at any time between Visit 1 (vaccination) and Visit 5 (6-month follow-up visit) that COVID-19 symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19/MIS-C illness rather than vaccine reactogenicity. For details, see Section 8.10.7.

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. Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, study visits, blood sample collection/analysis, or other procedures may be halted or discontinued.

								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Obtain informed consent and assent (if appropriate)	X							
Assign participant number	X							If participant is from a prior Pfizer COVID-19 study, record the participant number of the prior study in the CRF.
Obtain demography and medical history data (including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result)	X							
Obtain documentation of all prior COVID-19 vaccines	X							Record details in the prior COVID-19 vaccination CRF.
Urine pregnancy test (if appropriate)	X							Refer to Section 8.3.5.
Confirm use of contraceptives (if appropriate)	X	X	X					Refer to Section 5.3.1.
Measure height and weight	X							
Perform clinical assessment	X	X	X	X	X			Including, if indicated, a physical examination (Section 8.3.1).
Record nonstudy vaccine information	X	X	X	X	X			Refer to Section 6.9.
Record prohibited medication use		X	X	X	X	X	X	Refer to Section 6.9.1.

								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Confirm eligibility	X							
Measure body temperature	X							
Review temporary delay criteria	X							
Nasal (midturbinate) swab for SARS-CoV-2 NAAT	X					X		
Blood sample for immunogenicity assessment	~50 mL / 10 mL	~20 mL / 10 mL	~50 mL / 10 mL	~20 mL / 10 mL	~20 mL / 10 mL	~20 mL / 10 mL*	~20 mL / 10 mL	50 mL/20 mL is to be collected from participants ≥18 years of age; 10 mL is to be collected from participants 12 through 17 years of age. *If the Potential COVID-19 Illness Visit is an in-person visit, a blood sample will be taken. Blood sample collection may be halted or discontinued upon notification by Pfizer.

								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Blood sample for PBMC isolation	~130 mL	~130 mL	~130 mL	~130 mL	~130 mL			Applicable at designated sites only with optional consent given by participants ≥18 years of age. See Section 8.2.2. Not applicable to Cohort 1 or Cohort 3.
Blood sample for HLA typing	~5 mL							Applicable at designated sites only with optional consent given by participants ≥18 years of age. See Section 8.2.2. Not applicable to Cohort 1 or Cohort 3.
Obtain randomization number using the IRT system	X							
Obtain the participant's vaccine vial allocation using the IRT system	X							
Administer study intervention	X							Refer to Section 6.1.1.
Assess acute reactions for at least 30 minutes after study intervention administration	X							

								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Explain participant communication methods (including for COVID-19 illness and reactogenicity e-diary completion and severe reactogenicity symptoms), assist the participant or participant's parent(s)/legal guardian with downloading the app or issue provisioned device, if required	X							
Provide thermometer and measuring device	X							
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection (or collection by parent/legal guardian) of nasal swabs	X	X	X	X				
Ask/remind the participant or participant's parent(s)/legal guardian to contact the site if participant experiences any severe (Grade 3) reactogenicity symptoms	X	X						
Ask/remind the participant or participant's parent(s)/legal guardian to contact the site if a medically attended event or hospitalization occurs	X	X	X	X				

								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Ask/remind the participant or participant's parent(s)/legal guardian to contact site immediately if participant experiences any symptoms as detailed in Section 8.10.7 (COVID-19/MIS-C surveillance)	X	X	X	X				
Ask/remind the participant or participant's parent(s)/legal guardian to contact site immediately if participant experiences any symptoms of acute chest pain, shortness of breath, or palpitations	X	X						Refer to Section 8.10.11.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	←	→						If Visit 2 occurs on Day 6, continue to review e-diary data through Day 7.
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	Includes nonserious AEs through Visit 3, any AEs occurring up to 48 hours after a blood draw or nasal swab collection, and SAEs through the end of study (see Section 8.4.1).

								Notes
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**Unplanned**	**Unplanned**	
Visit Description	**Vax 1 Visit**	**1-Week Follow-Up Visit (Vax 1)**	**1-Month Follow-Up Visit (Vax 1)**	**3-Month Follow-Up Visit (Vax 1)**	**6-Month Follow-Up Visit (Vax 1)**	**Potential COVID-19 Illness Visit**	**Potential COVID-19 Convalescent Visit**	**The COVID-19 illness visit may be conducted as an in-person or telehealth visit.** The COVID-19 illness visit is only conducted for symptomatic participants. See Section 8.10.7.
Visit Window	**Day 1**	**6 to 8 Days After Visit 1**	**28 to 35 Days After Visit 1**	**84 to 98 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**	
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)						X	X	
Assist the participant or participant's parent(s)/legal guardian to delete the e-diary application or collect the provisioned device					X			

Abbreviations: CRF = case report form; HLA = human leukocyte antigen; IRT = interactive response technology; MIS-C = multisystem inflammatory syndrome in children; NAAT = nucleic acid amplification test; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2. INTRODUCTION

BNT162b2 (Comirnaty) is an RNA-based vaccine that, as of April 2022, has been granted full marketing authorization, conditional marketing authorization, EUA, or temporary authorization in a total of more than 140 countries for the prevention of COVID-19 caused by SARS-CoV-2.[1] In the US, it has been fully licensed for use in individuals 16 years of age and above as of 23 August 2021.[2] A third dose of BNT162b2 has been granted EUA in the US and many other countries to reduce the risk of infection in light of emerging new SARS-CoV-2 variants and increasing incidence of COVID-19 disease.[3,4,5] In the US, a fourth dose has been granted EUA for individuals 50 years of age and older as well as for individuals 12 years of age and older with certain kinds of immunocompromising conditions.[6]

The vaccine encodes the spike protein with a modRNA, is encapsulated in RNA-LNPs, and has demonstrated potent immunogenicity, high VE, and a favorable safety profile in Phase 1, 2, and 3 human trials,[7] as well as in real-world usage.[8] As SARS-CoV-2 continues to circulate at very high levels,[9] Pfizer/BioNTech are investigating next-generation, RNA-based COVID-19 vaccines, including BNT162b5 Bivalent (WT/OMI BA.2), to further protect against COVID-19 caused by emergent and potentially more antigenically diverse VOCs. BNT162b2 Bivalent vaccines targeting Omicron sublineages that are of growing concern, such as Omicron BA.4 and BA.5, are also being investigated by Pfizer/BioNTech to inform future development of booster vaccinations.

2.1. Study Rationale

Since the start of the pandemic, several VOCs have emerged, causing surges in infection rates, despite uptake of vaccines. Currently, the SARS-CoV-2 Omicron variant B.1.1.529 remains dominant in many countries though the prevalence of its sublineages has rapidly changed in recent months.[9] Within the US, as of the week ending 28 May 2022, BA.2 and BA.2.12.1 accounted for close to 91.5% of sequenced COVID-19 cases, while as of the week ending 13 August 2022, the BA.4 and BA.5 sublineages were responsible for 94.1% of all sequenced COVID-19 cases.[10] The UK Health Security Agency reports that the effectiveness of ChAdOx1-S, BNT162b2, and mRNA-1273 (pooled analysis) against hospitalization is 88% (range, 78%-93%) for the Omicron variant 2 or more weeks after a booster dose.[11] However, other studies have demonstrated that the effectiveness of BNT162b2 against SARS-CoV-2 infection and COVID-19 disease wanes over a period of months, particularly in the context of VOCs.[12,13,14] In light of the waning effectiveness of the primary 2-dose series of BNT162b2 as well as the existence of VOCs with cumulative mutations in the spike protein that are resilient to the existing immune response, particularly the Omicron variant, development of an enhanced bivalent vaccine that could generate an improved immune response, including against VOCs, could help better protect individuals against COVID-19.

Based on this rationale, Pfizer-BioNTech will evaluate in this study a vaccine candidate, BNT162b5 Bivalent (WT/OMI BA.2), which is an enhanced version of BNT162b2 Wild Type (ancestral strain, Wuhan-Hu-1; USA-WA1/2020) combined with BNT162b5

OMICRON (BA.2 sublineage), which has been designed to produce an improved antibody response against SARS-CoV-2.

BNT162b5 Bivalent (WT/OMI BA.2) uses the same modRNA platform, manufacturing processes, and LNP formulation as BNT162b2. Its active substance is a modified version of the mRNA segment used in BNT162b2 encoding the spike protein of SARS-CoV-2.

Because of the emergence of other Omicron sublineages, such as Omicron BA.4 and BA.5, which alone account for 5.3% (BA.4) and 88.8% (BA.5) of sequenced COVID-19 cases as of the week ending 13 August 2022,[10] and in line with a request by the FDA to begin clinical trials with modified vaccines containing an Omicron BA.4/BA.5 component,[15] a second cohort of approximately 500 participants has been added to the study in Protocol Amendment 1 to evaluate BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants ≥12 years of age. Cohort 2 will also investigate a higher dose (60 µg) of BNT162b2 (WT/OMI BA.4/BA.5) in participants ≥18 years of age. A third cohort of approximately 400 participants has been added to the study in Protocol Amendment 2 in order to have sufficient power to evaluate BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose in BNT162b2-experienced participants ≥18 years of age. BNT162b2 Bivalent (WT/OMI BA.4/BA.5) consists of the original SARS-CoV-2 spike protein mRNA, targeting the ancestral strain of the virus, in combination with mRNA encoding the spike protein of the Omicron variant (BA.4/BA.5 sublineage).

2.2. Background

SARS-CoV-2, a novel β-coronavirus, is a highly transmissible and pathogenic respiratory virus responsible for the ongoing COVID-19 pandemic. Studies of SARS-CoV-2 and SARS-CoV, a closely related coronavirus that caused the 2003 SARS pandemic, demonstrated that effective antibody protection could be achieved through spike protein–specific antibodies.[16,17] Therefore, vaccines targeting the spike protein of SARS-CoV-2 have been used as a critical mitigation strategy of the COVID-19 pandemic. However, waning effectiveness of the authorized vaccines has been shown to occur over time and is due to the emergence of VOCs.

A large study conducted in 10 states within the US noted waning mRNA vaccine effectiveness against emergency room and urgent care encounters as well as hospitalizations, when comparing 2 months versus ≥4 months after receipt of a third dose. During the Omicron period, VE against emergency room or urgent care visits was 87% during the first 2 months after a third dose and decreased to 66% among those vaccinated 4 to 5 months earlier; VE against hospitalizations was 91% during the first 2 months following a third dose and decreased to 78% ≥4 months after a third dose.[13] In another large study conducted in approximately 2.5 million UK adults vaccinated with either ChAdOx1, BNT162b2, or mRNA-1273, approximately 80% of the participants with SARS-CoV-2 had Omicron variant infections and approximately 20% had Delta variant infections. In those who received 3 doses of BNT162b2, VE increased to 67.2% at 2 to 4 weeks before declining to 45.7% at 10 or more weeks.[14]

A recent laboratory study in Israel compared the neutralization of Omicron-infected cells in serum samples obtained from participants who had received 2 doses of BNT162b2 with neutralization in samples obtained from participants who had received 3 doses of BNT162b2. The neutralization efficiency of BNT162b2 was also tested against wild-type SARS-CoV-2 and the Beta, Delta, and Omicron variants. The importance of a third vaccine dose was evidenced by a higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose compared to the second dose. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.[18] Moreover, the Omicron sublineages BA.4 and BA.5 have demonstrated substantial immune escape from neutralizing antibodies induced by both infection and immunization,[19] which has been attributed to the L452R and F486V spike mutations within the protein sequence of BA.4 and BA.5.[20]

BNT162b5 encodes an enhanced version of the original SARS-CoV-2 spike protein mRNA that has been shown to exhibit increased thermostability of the prefusion conformation and improved immunogenicity compared to BNT162b2. Immunization of naïve mice by this version of the mRNA formulated in LNPs elicited higher neutralization titers toward the ancestral strain and VOCs (Beta, Delta, and Omicron) than BNT162b2. The addition of a booster dose with an enhanced bivalent vaccine targeting the ancestral strain and Omicron variant may improve protection against SARS-CoV-2 infection, particularly against the currently dominant VOCs. A recommendation issued by the FDA on 30 June 2022 described the need to modify existing vaccines to address circulating variants and requested manufacturers to begin clinical trials with modified vaccines containing an Omicron BA.4/BA.5 component.[15] The additional studies to evaluate BNT162b bivalent vaccines, targeting emerging Omicron sublineages and other VOCs, may further inform decision-making for future booster vaccinations as the pandemic further evolves.

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.[21] The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age, healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. The study consists of 2 parts: Phase 1: to identify the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg [for BNT162b1]); Phase 2/3: an expanded-cohort and efficacy part to evaluate the selected vaccine candidate (BNT162b2).

The immunogenicity data from Phase 1 participants showed that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response. BNT162b2 was selected from the Phase 1 part of the study based on the overall safety, tolerability, and immunogenicity. In a mid–November 2020 analysis of 36,621 participants

randomized 1:1 to vaccine or placebo and who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination schedule, the efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the active vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.[22]

In a subsequent analysis of 927 confirmed symptomatic cases of COVID-19, an efficacy rate of 91.3% was observed for BNT162b2 in preventing such cases occurring between 7 days and 6 months after the second dose.[23] Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

- 100% in preventing severe disease as defined by the CDC.
- 95.3% in preventing severe disease as defined by the FDA.
- 100% in preventing COVID-19 cases in South Africa, where the B.1.351 lineage is prevalent.

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled through the 14 November 2020 data cutoff (N = 43,252), which includes late enrollment of additional adolescent and adult participants, were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.[22]

A booster dose (Dose 3) of BNT162b2 was administered to 306 Phase 3 participants without prior evidence of SARS-CoV-2 infection ~6 months after completing the 2-dose schedule. The immune response 1 month after administration of Dose 3 was noninferior to that observed 1 month after Dose 2 in the same participants. Furthermore, from the same analysis, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3, a high proportion of participants (99.5%) had a seroresponse at 1 month after Dose 3 compared with 98.0% at 1 month after Dose 2.[7]

On 22 September 2021, based on safety and immunogenicity data from approximately 300 immunocompetent adult booster dose recipients from Study C4591001, the FDA issued the EUA for a single booster dose of BNT162b2 30 µg for 1) individuals 65 years of age and older; 2) individuals 18 through 64 years of age at high risk of severe COVID-19; and 3) individuals 18 through 64 years of age whose frequent institutional or occupational

exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.[24] On 19 November 2021, the FDA amended the EUA, authorizing use of a single booster dose for all individuals 18 years of age and older after completion of primary vaccination with an FDA-approved COVID-19 vaccine.[25]

On 09 December 2021, the FDA again amended the EUA to authorize the use of a single booster dose for administration to individuals 16 and 17 years of age at least 6 months after completion of primary vaccination with BNT162b2.[3] In addition, a booster dose of the vaccine is authorized in the EU and other countries, with recommendations for populations varying based on local health authority guidance.[4,5]

The per-protocol interim safety and efficacy analysis was conducted in October 2021 for Study C4591031 Substudy A. In this study, approximately 10,000 participants who had previously received 2 doses of BNT162b2 as a primary series in Study C4591001 were randomized 1:1 in Study C4591031 to receive either a 30-µg booster dose (the same dosage strength as in the 2-dose primary series) or placebo. The time between the second dose and administration of the booster dose or placebo for most participants was ≥10 to <12 months.

Symptomatic COVID-19 occurrence was measured from ≥7 days after booster or placebo, with a median follow-up of 2.5 months. During the blinded placebo-controlled study period up to a data cutoff date of 05 October 2021, there were a total of 6 cases of COVID-19 in the booster group and 123 cases in the nonboosted placebo group, in the evaluable efficacy population without evidence of prior SARS-CoV-2 infection. The observed relative VE was 95.3% (2-sided 95% CI: 89.5%, 98.3%), which reflects the reduction in disease occurrence in the boosted group versus the nonboosted group. The AE profile was generally consistent with other previously submitted clinical safety data for the vaccine, with no new safety concerns identified. No cases of myocarditis or pericarditis were reported.[26]

C4591031 Substudy E is an ongoing Phase 3 trial in approximately 2900 participants 18 years of age and older who have previously received 3 doses of BNT162b2 (30-µg dose). Participants in this substudy received a fourth dose of either BNT162b2 or BNT162b2 OMICRON (BA.1 sublineage) or a combination of both at a total dose level of either 30 µg or 60 µg. From the available safety data from this study, in participants 18 through 55 years of age, the monovalent Omicron-modified vaccine (at a 30-µg dose level) showed a similar local and systemic reactogenicity event profile as the prototype BNT162b2 vaccine at the same dose level. In participants >55 years of age, monovalent and bivalent Omicron-modified vaccines at the 30-µg dose level showed a similar local and systemic reactogenicity event profile as the prototype BNT162b2 vaccine. In the older age group at the 60-µg dose level, mild to moderate injection site pain, fatigue, and muscle pain were more common compared to the 30-µg dose level. In participants >55 years of age, without evidence of COVID-19 infection, Omicron BA.1 neutralization activity substantially increased with Omicron-modified bivalent vaccines as a fourth dose. Moreover, the Omicron-modified variant vaccines as a fourth dose elicit improved Omicron response against the Omicron BA.4/BA.5 sublineages, albeit at a lower level compared to the response against Omicron BA.1.[27]

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and BNT162b5 Bivalent (WT/OMI BA.2) have not been administered to humans before; however, they are highly similar to the combination vaccine under evaluation in C4591031 Substudy E. Therefore, this study will be performed as a Phase 2/3 study focusing on the humoral immune response and safety of this vaccine.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with several SARS-CoV-2 vaccines now in use under marketing authorizations or EUAs. The available safety and immunogenicity data from ongoing Pfizer-BioNTech clinical trials and real-world effectiveness and safety data, combined with available nonclinical data with BNT162 vaccines and data from nonclinical and clinical trials with the same or related RNA components or antigens, support a favorable benefit/risk profile and support continued clinical development of BNT162b5 and BNT162b2 bivalent vaccines.

Continued clinical investigation is justified, given:

- The threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection.
- The threat posed by the SARS-CoV-2 variants emerging worldwide.
- The potential need for enhancing immune responses to overcome waning immunity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the study interventions may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Interventions: BNT162b2 Bivalent and BNT162b5 Bivalent RNA-Based COVID-19 Vaccine Candidates		
For BNT162b2: Key identified risks for BNT162b2 include local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, muscle pain, and joint pain. Other key risks identified for BNT162b2 are lymphadenopathy; hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema, and anaphylaxis; and myocarditis and pericarditis. For BNT162b2 OMICRON (BA.1 sublineage) and BNT162b2 OMICRON (BA.4/BA.5 sublineage): This vaccine has the same modRNA platform (with sequence changes limited to those that are Omicron-specific) and LNP formulation as BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2. For BNT162b5 and BNT162b5 OMICRON (BA.2 sublineage): This vaccine has the same modRNA platform (with sequence changes intended to enhance the immune response [BNT162b5] and that are Omicron-specific [BNT162b5 OMICRON (BA.2 sublineage)]) and LNP formulations as BNT162b2; therefore, the safety profile is expected to be similar.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. Data available from the C4591001 study showed low incidence of severe or serious events and no clinically concerning safety observations across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[22] Data available from the C4591031 Substudy E showed that mild to moderate injection site pain, fatigue, and muscle pain were more common following a 60-µg dose compared to a 30-µg dose. Anaphylaxis: Frequency not known. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Local reactions and systemic events will be recorded using a reactogenicity e-diary to monitor local reactions and systemic events in real time. Collection of AEs from signing of the ICD through 1 month and SAEs through 6 months after study vaccination. DMC review throughout the study to review all safety data. Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.10.11.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Postauthorization safety data surveillance has confirmed the safety profile observed in Study C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in the SRSD.	
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Monitoring for cases of COVID-19 developing during the study as part of the COVID-19 surveillance.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in the study may be:

- Receipt of a further dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey better protection against the SARS-CoV-2 wild-type (ancestral) strain and/or VOCs during a global pandemic.
- Access to COVID-19 diagnostic testing.
- Contributing to research to help others in a time of global pandemic.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants as stated in Section 2.3.1, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccines are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Refer to Table 1 and Table 3 for details of the Cohort 2 group and Cohort 3 group, respectively.

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Objectives	Estimands	Endpoints
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers

Objectives	Estimands	Endpoints
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[d] or 60 µg[d] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55[d], and >55[d] years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Exploratory		
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases

Objectives	Estimands	Endpoints
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[e] and at the convalescent visit.		• SARS-Cov-2–neutralizing titers previously specified for the respective cohorts
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to emerging VOCs.		• SARS-CoV-2–neutralizing titers for VOCs not already specified
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[b] and Omicron in a subset of participants with PBMC samples collected.		

a. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. Reference strain is also referred to as the Wild Type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
c. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
d. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.
e. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent vaccines. The study duration for each participant will be approximately 6 months. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan.

Refer to the schema in Section 1.2.

Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed and study visits or other procedures may be discontinued.

An EDMC will review cumulative unblinded data throughout the study. Refer to Appendix 1, Section 10.1.5.1.

Cohort 1 Design

For the purposes of this protocol, study intervention within this cohort refers to:

- BNT162b5 Bivalent (WT/OMI BA.2) 30 µg
- BNT162b2 Bivalent (WT/OMI BA.1) 30 µg

Participants 18 through 55 years of age will be randomized at a ratio of 1:1 to receive a single 30-µg dose of 1 of the 2 study interventions as a second booster dose. Participants will be stratified by the number of months since the last dose of COVID-19 vaccine received prior to randomization (3 to 6 months [90 to 180 days] or >6 months [>180 days]). Approximately 200 participants will be enrolled in this cohort.

Cohort 2 Design

For the purposes of this protocol, study intervention within this cohort refers to:

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg
- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg

Participants 12 through 17 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label). Participants 18 through 55 and >55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will be randomized 1:1 within each age group to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg as a second booster dose (observer-blind). Approximately 500 participants will be enrolled into this cohort per Table 1.

Table 1. Cohort 2 Design

Cohort 2: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	12-17 years	3	150-365 days	30 µg	100	Open-label
2	18-55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
3	18-55 years	3	150-365 days	60 µg	100	
4	>55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
5	>55 years	3	150-365 days	60 µg	100	

To evaluate the immunogenicity objective for Cohort 2, a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from the C4591031 Substudy E expanded cohort who received Bivalent BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected as the control group for the descriptive immunogenicity summary (Table 2). The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.

Table 2. Cohort 2 Immunogenicity Control Groups From C4591031 Substudy E

C4591031 Substudy E Subset			
Participant Age Group	**Vaccine Group**	**Dose**	**Number of Participants**
18-55 years	Bivalent BNT162b2 (WT/OMI BA.1)	30 µg	100
18-55 years	Bivalent BNT162b2 (WT/OMI BA.1)	60 µg	100
>55 years	Bivalent BNT162b2 (WT/OMI BA.1)	30 µg	100
>55 years	Bivalent BNT162b2 (WT/OMI BA.1)	60 µg	100

Note: Vaccine group name in C4591031 Substudy E is "Bivalent BNT162b2 and BNT162b2 OMI".

Cohort 3 Design

For the purposes of this protocol, study intervention within this cohort refers to:

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg

Participants 18 years of age and older who have received 3 prior 30-µg doses of BNT162b2, with the most recent dose being 150 to 365 days prior to Visit 1 (Day 1), will receive a single 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) as a second booster dose (open-label). Approximately 400 participants will be enrolled into this cohort per Table 3.

Table 3. Cohort 3 Design

Cohort 3: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	18-55 years	3	150-365 days	30 µg	200	Open-label
2	>55 years	3	150-365 days	30 µg	200	Open-label

Note: For certain safety and immunogenicity objectives, the 18- through 55-age group and the >55-age group will comprise participants from Cohorts 2 and 3 combined.

Combining Cohort 2 and Cohort 3, there will be approximately 300 participants in each age group who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg. To evaluate the primary immunogenicity hypothesis for the >55-age group of Cohort 2 and Cohort 3 combined, the participants >55 years of age from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group (approximately 300 participants [Expanded Enrollment – Group 1]).

4.2. Scientific Rationale for Study Design

The immune response following vaccination with BNT162b2 has been observed to wane with time, and a booster dose of BNT162b2 has demonstrated improvement in immune response, albeit to a lesser degree against some variants, particularly Omicron, of the original SARS-CoV-2 virus. This is the first clinical study of BNT162b5 Bivalent (WT/OMI BA.2) aimed to improve the current protection elicited by BNT162b2. It is also the first clinical study of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to evaluate the immune response to this new VOC-targeted vaccine. Because of the similarity between the bivalent vaccines used in this study and the bivalent vaccine currently being studied in C4591031 Substudy E (BNT162b2 Bivalent [WT/OMI BA.1]) and because there have been no safety concerns to date with that vaccine, this is a Phase 2/3 study. Prospective capture of confirmed COVID-19 cases with active COVID-19 surveillance and convalescent visits has been included.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), in the age group of the study, to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

Given the relatively small size of the study, there may be less representation with respect to race, ethnicity, and geographic location.

4.2.2. Choice of Contraception/Barrier Requirements

BNT162b2 is approved for use without any contraceptive precautions. All investigational vaccines included in this study are RNA-LNP vaccines utilizing modRNA. While there is no suspicion of human teratogenicity based on the intended pharmacology, some of the variant vaccine components under evaluation have not been administered to humans before and, therefore, contraception requirements have been included in this protocol. See Appendix 4 for contraception requirements.

4.3. Justification for Dose

Based on data from the Phase 1 component of clinical trial C4591001 and available nonclinical data, the modRNA BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2/3 evaluation of safety, immunogenicity, and efficacy after 2 doses administered 3 weeks apart and is the authorized dose level for the third dose administered at least 5 months following the second dose. The 30-µg dose level of BNT162b2 was shown to be effective and has been approved in multiple countries worldwide for the primary 2-dose series as well as for third and fourth (booster) doses.

Cohort 2 will also investigate a higher dose (60 µg) of BNT162b2 (WT/OMI BA.4/BA.5) in participants ≥18 years of age. Clinical trial C4591031 Substudy E is an ongoing study including participants 18 years of age and older who have previously received 3 doses of BNT162b2 (30-µg dose). A subset of participants in this substudy received BNT162b2 Bivalent (WT/OMI BA.1) at a total dose level of either 30 µg or 60 µg as a second booster dose. From the available safety data from the study, the reactogenicity profile of the variant vaccines was overall similar to the prototype BNT162b2 vaccine. In participants >55 years of age, who received monovalent and bivalent Omicron-modified vaccines at the 60-µg dose level, mild to moderate injection site pain, fatigue, and muscle pain were more common compared to the 30-µg dose level.[27] A subset of participants from C4591031 Substudy E (≥18 years of age) who received BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be randomly selected to achieve the primary immunogenicity objective of Cohort 2.

4.4. End of Study Definition

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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. Ages for each cohort as follows:

   Cohort 1: Participants 18 through 55 years of age at randomization.

   Cohort 2: Participants ≥12 years of age at Visit 1.

   Cohort 3: Participants ≥18 years of age at Visit 1.

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

Participant and Disease Characteristics:

2. Participants and participants' parent(s)/legal guardian(s), as appropriate, willing and able to comply with all scheduled visits/contacts, investigational plan, laboratory tests, 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 signed informed consent/assent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

   The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian (as defined in Appendix 1, Section 10.1.3) and the participant's assent, when applicable, before any study-specific activity is performed. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

Other Inclusion Criteria:

5. Cohort 1: Participants who have received 1 booster dose of a US-authorized COVID-19 vaccine, with the last prior dose being 90 or more days before Visit 1 (Day 1).

   Note: Documented confirmation of prior COVID-19 vaccines received must be obtained prior to randomization. All prior COVID-19 vaccines must be authorized for use in the US.

   Cohort 2 and Cohort 3: Participants who have received 3 prior doses of 30 µg BNT162b2, with the last dose being 150 to 365 days before Visit 1 (Day 1).

   Note: Documented confirmation of prior doses of BNT162b2 received must be obtained prior to randomization.

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

4. Women who are pregnant or breastfeeding.

5. 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.

Prior/Concomitant Therapy:

6. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease), or radiotherapy, within 60 days before enrollment or planned receipt through conclusion of the study.

   Note: Chronic systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

Prior/Concurrent Clinical Study Experience:

8. Participation in other studies involving receipt of a study intervention within 28 days before randomization. Anticipated participation in other studies involving a study intervention from randomization through the end of this study.

Other Exclusion Criteria:

9. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant 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 acceptable 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, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant or participant's parent(s)/legal guardian to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, 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 enrolled in the study. 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, and any SAEs.

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/Administration of Study Intervention

The following conditions may allow a participant to receive study intervention once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

1. A positive SARS-CoV-2 test result (NAAT or rapid antigen test) within the previous 28 days.

2. Current febrile illness (body temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration. This includes symptoms that could represent a potential COVID-19 illness (refer to Section 8.10.7).

   Note: The participant should be directed to seek additional testing through his/her primary healthcare provider at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

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

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

5. 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(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to investigational product.

6.1. Study Interventions Administered

Cohort 1

- BNT162b5 Bivalent (WT/OMI BA.2) =

  BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529) sublineage BA.2

  (BNT162b5 RNA-LNP vaccine utilizing modRNA and encoding the P6' S)

- BNT162b2 Bivalent (WT/OMI BA.1) =

  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.1

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 1		
Intervention Name	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type[a] and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2]) Preformulated as a single vial (no dilution required)	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1]) Preformulated as a single vial (no dilution required)
Arm Name **(group of participants receiving a specific study intervention or no study intervention)**	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Type	Vaccine	Vaccine
Dose Formulation	Multidose vial[b]	Multidose vial[b]
Unit Dose Strength(s)	100 µg/mL	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b5 Wild Type[a] and 15 µg BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	30 µg (15 µg BNT162b2 Wild Type[a] and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])

Study Interventions – Cohort 1		
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental and active comparator
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Pfizer	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vial will be labeled as required per country requirement.	Study intervention will be provided in a glass vial as open-label supply. Vial will be labeled as required per country requirement.

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.
b. Study intervention will be administered as a single dose from multidose vials.

Study Arms – Cohort 1		
Arm Title	BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b2 Bivalent (WT/OMI BA.1)
Arm Type	Experimental	Experimental and active comparator
Arm Description	Participants will receive 30 µg of BNT162b5 Bivalent (WT/OMI BA.2) at Visit 1.	Participants will receive 30 µg of BNT162b2 Bivalent (WT/OMI BA.1) at Visit 1.
Associated Intervention Labels	BNT162b5 Bivalent (WT/OMI BA.2) (BNT162b5 Wild Type and BNT162b5 OMICRON [B.1.1.529 sublineage BA.2])	BNT162b2 Bivalent (WT/OMI BA.1) (BNT162b2 Wild Type and BNT162b2 OMICRON [B.1.1.529 sublineage BA.1])

Cohort 2

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) =

  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 2	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name (group of participants receiving a specific study intervention or no study intervention)	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Type	Vaccine
Dose Formulation	Multidose vial[b]
Unit Dose Strength(s)	100 µg/mL

Study Interventions – Cohort 2	
Dosage Level(s)	30 µg or 60 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) (30 µg BNT162b2 Wild Type and 30 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vial will be labeled as required per country requirement.

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.
b. Study intervention will be administered as a single dose from multidose vials.

Study Arms – Cohort 2					
Arm Title	Group 1: 12-17 years, 30 µg	Group 2: 18-55 years, 30 µg	Group 3: 18-55 years, 60 µg	Group 4: >55 years, 30 µg	Group 5: >55 years, 60 µg
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg at Visit 1
Associated Intervention Label	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])				

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Cohort 3

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5) =

  BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5

  (BNT162b2 RNA-LNP vaccine utilizing modRNA and encoding the P2 S)

Study Interventions – Cohort 3	
Intervention Name	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5]) Preformulated as a single vial (no dilution required)
Arm Name **(group of participants receiving a specific study intervention or no study intervention)**	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
Type	Vaccine
Dose Formulation	Multidose vial[b]
Unit Dose Strength(s)	100 µg/mL
Dosage Level(s)	30 µg (15 µg BNT162b2 Wild Type and 15 µg BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by Pfizer
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Vial will be labeled as required per country requirement.

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.
b. Study intervention will be administered as a single dose from multidose vials.

Study Arms – Cohort 3		
Arm Title	Group 1: 18-55 years of age, 30 µg	Group 2: >55 years of age, 30 µg
Arm Type	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1
Associated Intervention Label	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])	

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 1 in accordance with the study's SoA (Section 1.3).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. The volume to be administered may vary by dose level; full details are described in the IPM.

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, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) 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, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM for storage conditions of the study intervention once prepared.

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff 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 IPM. 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 IPM.

6.2.1. Preparation and Dispensing

See the IPM 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 will be prepared by qualified unblinded site personnel according to the IPM. The study intervention will be administered by unblinded study staff to all participants.

Study intervention will be provided in multidose vials; however, they are intended for single use, as outlined in the IPM.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system, including Group 1 of Cohort 2 (12 through 17 years of age) and the Cohort 3 groups, all receiving 30 µg of BNT162b2 Bivalent (WT/OMI BA.4/BA.5). Participants in Cohort 1 will be randomized 1:1 to receive either BNT162b5 Bivalent (WT/OMI BA.2) 30 µg or BNT162b2 Bivalent (WT/OMI BA.1) 30 µg. Participants 18 through 55 and >55 years of age in Cohort 2 will be randomized 1:1 within each age group to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg. 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 randomization number corresponding to the assigned vaccine group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Participants will be stratified in Cohort 1 by the number of months since the last dose of the COVID-19 vaccine received prior to entering the study (3 to 6 months [90 to 180 days] or >6 months [>180 days]).

Study intervention will be dispensed at the study visits summarized in the SoA.

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

6.4. Blinding

Cohort 1: This cohort will be observer-blind at the site level with respect to study intervention allocation and open-label to most Pfizer staff. Refer to Section 6.4.3.

Cohort 2: Participants 18 through 55 and >55 years of age receiving the second booster: These participant groups will be observer-blind at the site level with respect to study intervention allocation (dose of BNT162b2 [WT/OMI BA.4/BA.5]) and open-label to most Pfizer staff.

Participants 12 through 17 years of age receiving the second booster: This participant group is open-label. Refer to Table 1.

Cohort 3: Both participant groups (18 through 55 years of age and >55 years of age) receiving the second booster are open-label. Refer to Table 3.

6.4.1. Blinding of Participants

Cohort 1: Participants will be blinded to their assigned study intervention.

Cohort 2: Participants 12 through 17 years of age receiving the second booster will not be blinded to study intervention. Participants 18 through 55 and >55 years of age receiving the second booster will be blinded to the dose of BNT162b2 (WT/OMI BA.4/BA.5).

Cohort 3: All participants receiving the second booster will not be blinded to study intervention.

6.4.2. Blinding of Site Personnel

Although Cohort 2 has an open-label group (12 through 17 years of age receiving their second booster) and both Cohort 3 groups are open-label, the following instructions for site personnel applies to all participants in order to maintain the blinding for the other cohorts/groups:

In this observer-blind 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 there are differences in physical appearance of the study interventions, the study intervention will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The study will be unblinded to site personnel at a time decided by Pfizer.

6.4.3. Blinding of the Sponsor

Cohort 1 and Cohort 2: To facilitate rapid review of data in real time, the majority of Pfizer/BioNTech staff will be unblinded to study intervention allocation.

Cohort 3: Given the single study intervention arm, both groups are unblinded to the majority of Pfizer staff involved in the conduct of the study.

All Cohorts: All laboratory testing personnel will remain blinded to study intervention assigned/received throughout the study.

6.4.4. 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 vaccine 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 study medical monitor 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, Pfizer 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 IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the unblinded 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 ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from Pfizer and/or designee.

6.6. Dose Modification

Not applicable to this study.

6.7. Continued Access to Study Intervention After the End of the Study

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

6.8. 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 study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

6.9. Prior and Concomitant Therapy

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

- Prohibited medications listed in Section 6.9.1 will be recorded in the concomitant medication CRF.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.
- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.
- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

6.9.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per Section 7.2). 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. With the exception of seasonal and pandemic influenza vaccine that 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 (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment through conclusion of the study.

  Note: Chronic systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent.

- Receipt of systemic corticosteroids for <14 days is prohibited from 28 days prior to enrollment through 28 days after administration of study intervention.
- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration through conclusion of the study.

- Receipt of any other (nonstudy) coronavirus vaccine at any time during study participation.

- 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.

6.9.2. Permitted During the Study

- Medication other than that described as prohibited in Section 6.9.1 required for treatment of preexisting conditions or acute illness is permitted.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request or request of the participant's parent(s)/legal guardian. The participant will be permanently discontinued from the study at that time. Reasons for discontinuation from the study include the following:

- Lost to follow-up;

- Death;

- Study terminated by Pfizer;

- AEs;

- Participant/participant's parent(s)/legal guardian request;

- Investigator request;

- Select protocol deviations (Note: receipt of a COVID-19 vaccine outside of the study will result in study withdrawal).

If a participant withdraws from the study, they or the participant's parent(s)/legal guardian 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 Pfizer 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 will be performed and no additional data will be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

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 or participant's parent(s)/legal guardian specifically withdraws consent/assent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants or participants' parent(s)/legal guardian 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 study procedures and/or postvaccination 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 the participant 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 return to the clinic for a required study visit:

- The site must attempt to contact the participant or participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible. Counsel the participant or participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule, and ascertain whether 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 or participant's parent(s)/legal guardian (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 or participant's parent(s)/legal guardian continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline 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 date of birth will be collected to critically evaluate the immune response and safety profile by age.

A participant number will be assigned.

A randomization number and study intervention allocation will be obtained from the IRT system.

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

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 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 they have 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.

Safety and laboratory results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 at scheduled visits in this study is approximately 160 mL for participants ≥18 years of age and 50 mL for participants 12 through 17 years of age. Those participants ≥18 years of age in Cohort 2 who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume

of up to approximately 815 mL. Additionally, 20 mL of blood for participants ≥18 years of age and 10 mL for participants 12 through 17 years of age will be taken at an unplanned in-person potential COVID-19 illness visit and at an unplanned COVID-19 convalescent visit, conducted 28 to 35 days following the illness visit, with the illness visit completed at any time a participant develops symptoms indicating potential COVID-19. 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 56 consecutive days for participants 18 years of age and older.

8.1.1. Baseline Procedures

The baseline procedures (not detailed in subsequent sections) are listed below. They are performed at Visit 1 (Day 1):

- Record demography data (including date of birth, sex, race, and ethnicity).
- Record any medical history of clinical significance.
- Measure and record height and weight.

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Surveillance for COVID-19

Surveillance for potential cases of COVID-19 and MIS-C will occur throughout a participant's involvement in the study to describe both COVID-19 (all participants) and MIS-C (participants <21 years of age). If, at any time, a participant develops acute respiratory illness (see Section 8.10.7), for the purposes of the study he or she will be considered to potentially have COVID-19. In this circumstance, the participant or participant's parent(s)/legal guardian should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using an 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 8.10.8) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
    - Fever;
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste or smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
- Confirmed severe COVID-19 (FDA definition[28]): confirmed COVID-19 and presence of at least 1 of the following:
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
    - Significant acute renal, hepatic, or neurologic dysfunction;
    - Admission to an ICU;
    - Death.

- Confirmed severe COVID-19 (CDC definition[29]): confirmed COVID-19 and presence of at least 1 of the following:
    - Hospitalization;
    - Admission to the ICU;
    - Intubation or mechanical ventilation;
    - Death.

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

Confirmed MIS-C definition, as per the CDC MIS-C case definition[30]:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, AKI);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
    - Dermatologic (eg, rash, mucocutaneous lesions);
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND
- No alternative plausible diagnoses; AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR

- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

8.2.2. Vaccine-Induced Immunogenicity

Blood samples will be obtained at each visit for immunogenicity testing at the central laboratory. The following assays will be performed on serum samples at each visit:

- SARS-CoV-2 neutralization assay (reference strain)

- SARS-CoV-2 neutralization assays (Omicron BA.1, Omicron BA.2, Omicron BA.4, Omicron BA.5; other VOCs, including other Omicron sublineages, may also be evaluated)

At designated sites, optional whole blood samples of ~130 mL will be obtained from up to approximately 30 participants per group (≥18 years of age only) within Cohort 2 for evaluation of boostability and protection against Omicron and the reference strain for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to Omicron and the reference strain. A blood sample of ~5 mL for HLA typing will also be obtained.

8.2.3. N-Binding Antibody Test.

The N-binding antibody test will be performed by the central laboratory on each blood sample to establish prior exposure to SARS-CoV-2 up to each time point. These data will be used for study analyses.

8.2.4. 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 analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. 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 vaccines under study in this protocol, to inform the development of other vaccines or vaccine-related products, and/or for vaccine-related assay work supporting vaccine programs.

No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant or participant's parent(s)/legal guardian may request that their 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, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

A complete physical examination will include 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.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2. Vital Signs

The participant's body temperature will be measured at Visit 1, prior to study vaccination.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.3.4. Electronic Diary

Participants or participants' parent(s)/legal guardian will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the personal device of the participant or participant's parent(s)/legal guardian. All participants or participants' parent(s)/legal guardian will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days from the day of 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. Generally, these data do not need to be reported by the investigator in the CRF as AEs. However, if a participant or participant's parent(s)/legal guardian withdraws because of events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

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

The investigator or designee must obtain stop dates from the participant or participant's parent(s)/legal guardian 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.

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[31]

8.3.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardian 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 or participant's parent(s)/legal guardian 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 4. 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 to the grading scale in Table 4.

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 Pfizer. A Grade 4 reaction will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the case report form.

8.3.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardian will be asked to assess vomiting, diarrhea, headache, fatigue/tiredness, 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 5.

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 Pfizer. A Grade 4 systemic event

will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Table 5. 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.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if the test result is positive, the symptoms should be recorded in the potential COVID-19 illness CRFs (with potential COVID-19 illness visit completed) rather than as systemic events in the reactogenicity e-diary (refer to Sections 8.10.7 and 8.10.8).

8.3.4.4. Fever

In order to record information on fever, a thermometer will be given to participants or participants' parent(s)/legal guardian 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. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 6 during analysis.

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 Pfizer. Fevers >40.0°C (>104.0°F) will be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (Section 10.3.3).

Table 6. Scale for Fever

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

8.3.4.5. Antipyretic/Analgesic Medication

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

8.3.5. 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 Visit 1, before the administration of the study intervention 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 not be administered the study intervention dose and will be withdrawn from the study.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 from the study (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant or participant's parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. 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 or participant's parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3 (approximately 1 month after the participant's study vaccination).

In addition, any AE occurring up to 48 hours after any subsequent blood draw or nasal swab collection must be recorded on the CRF.

SAEs will be collected from the time the participant or participant's parent(s)/legal guardian provides informed consent through Visit 5 (approximately 6 months after the participant's study vaccination).

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues 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 or participant's parent(s)/legal guardian 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 permanently discontinues or temporarily discontinues the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek information on 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 they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Reporting 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 its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant or participant's parent(s)/legal guardian.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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 or participant's parent(s)/legal guardian is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward 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.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant within 28 days after receiving study intervention.
- A male participant inseminates a female partner within 28 days after receiving study intervention.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by needlestick injury, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by needlestick injury, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting 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 28 days after the study intervention. Beyond 28 days after the study intervention, any pregnancy that occurs will not be considered EDP for this study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting 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 should be reported as an SAE;

- 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding within 28 days after receiving the study intervention.

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study,

so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

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

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

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

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

OR

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

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

8.4.8. Adverse Events of Special Interest

The following events are considered AESIs:

- Confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination. See Section 8.10.11.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.4.1 through Section 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Vaccination Errors

Vaccination 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.

Vaccination errors are recorded and reported as follows:

Recorded on the Vaccination Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the vaccination error	Only if associated with an SAE

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination 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 vaccination errors occurring to a study participant are to be captured on the vaccination error page of the CRF, which is a specific version of the AE page.

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

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

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

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.

8.9. Health Economics

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

8.10. Study Procedures

8.10.1. Visit 1 – Study Intervention Administration – Day 1

- Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent and assent, if appropriate, will be obtained from the participant and/or participant's parent(s)/legal guardian. 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 and/or participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. Ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination and on the day of the vaccination.

- Assign a participant number using the IRT system. If the participant is from a prior Pfizer COVID-19 study, record the participant number of the prior study in the CRF.

- 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 medical history, including confirmed COVID-19 diagnosis or asymptomatic positive SARS-CoV-2 test result (NAAT or antigen test), and any other medical history of clinical significance.

- Review documentation of all prior COVID-19 vaccinations. All vaccines must be authorized for use in the US for participants enrolled in Cohort 1. All prior vaccines must be 30-µg doses of BNT162b2 for participants enrolled in Cohort 2.

- Perform a urine pregnancy test on WOCBP as described in Section 8.3.5.

- Discuss contraceptive use as described in Section 5.3.1.

- Measure the participant's height and weight.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination (refer to Section 8.3.1), and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.

- Record nonstudy vaccinations as described in Section 6.9.

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

- On the day of and before vaccination, measure the participant's body temperature.

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

- On the day of and before vaccination, obtain a nasal (midturbinate) swab (collected by site staff).

- On the day of and before vaccination, collect a blood sample (approximately 50 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for testing of immunogenicity and N-binding antibody.

- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only; additional consent required), collect a blood sample (approximately 130 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.

- Blinded site staff will obtain the participant's randomization number and vaccine vial allocation using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle, preferably of the nondominant arm. Please refer to the IPM 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.

- Record AEs as described in Section 8.4.

- Explain the e-diary technologies available for this study (see Section 8.3.4) and assist the participant or participant's parent(s)/legal guardian in downloading the study application onto the participant's or participant's parent(s)/legal guardian's own device or issue a provisioned device if required.

- Provide instructions on e-diary completion and ask the participant or participant's parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination (see Section 8.3.4.1 through Section 8.3.4.5).

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

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

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

- Provide instructions on COVID-19 illness e-diary completion and ask the participant or participant's parent(s)/legal guardian to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 8.10.7 for further details. Provide instructions for use of the provided thermometer to monitor for fever (for COVID-19 surveillance).

- Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.11).

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

- Remind the participant or participant's parent(s)/legal guardian to bring the e-diary device 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.

8.10.2. Visit 2 – 1-Week Follow-Up Visit (6 to 8 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.

- Record nonstudy vaccinations as described in Section 6.9.

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.

- Record AEs as described in Section 8.4.

- Discuss contraceptive use as described in Section 5.3.1.

- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing.

- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day the reactogenicity e-diary was completed.

- If the 7-day reactogenicity period is ongoing: Remind the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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.

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

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any symptoms as detailed in Section 8.10.7.

- Ensure the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.10.11).

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

- If the 7-day reactogenicity period is ongoing: Remind the participant or participant's parent(s)/legal guardian 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.

8.10.3. Visit 3 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Confirm contraceptive use as described in Section 5.3.1.
- Collect a blood sample (approximately 50 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day the reactogenicity e-diary was completed and record stop dates in the CRF, if required.
- Remind the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any symptoms as detailed in Section 8.10.7.

- Ensure the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.

- 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.

8.10.4. Visit 4 – 3-Month Follow-Up Visit (84 to 98 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.

- Record nonstudy vaccinations as described in Section 6.9.

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.

- Record AEs as described in Section 8.4.

- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing, unless advised otherwise by Pfizer.

- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.

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

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any symptoms as detailed in Section 8.10.7.

- Ensure the participant has a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs or instruct the participant's parent(s)/legal guardian on the technique for collecting a nasal swab from their child at home.
- 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.

8.10.5. Visit 5 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 1)

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination, per Section 8.3.1, and record any findings in the source documents and, if clinically significant, record any findings on the AE CRF.
- Record nonstudy vaccinations as described in Section 6.9.
- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4.
- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age) for immunogenicity testing, unless advised otherwise by Pfizer.
- If the participant is part of the group for description of cell-mediated immune response (select sites only; Cohort 2 and ≥18 years of age only), collect a blood sample (approximately 130 mL) for PBMC isolation.
- Collect the participant's e-diary provisioned device or assist the participant or participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

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

If a Grade 3 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 0) 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 a suspected Grade 4 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 0) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

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

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or participant's parent(s)/legal guardian 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 that it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

8.10.7. COVID-19 and MIS-C Surveillance

The current list of COVID-19 symptoms according to the CDC can be found at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;

- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

The participant or their parent(s)/legal guardian(s) are also instructed to contact the site immediately should the participant receive a positive SARS-CoV-2 test (NAAT or rapid antigen) result that is not accompanied by any symptoms. A potential COVID-19 visit is not required in this instance, but details of the positive test should be recorded in the designated CRF.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.10.2) installed on a provisioned device or on the participant's or participant's parent(s)/legal guardian'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.

8.10.8. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant, the participant's parent(s)/legal guardian, and investigator to communicate on aspects of clinical care.

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

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.
- Record AEs as described in Section 8.4. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment only on the relevant pages of the CRF, as these are expected endpoints.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab or instruct the participant's parent(s)/legal guardian to collect a nasal swab from their child at home and ship for assessment at the central laboratory.
- If the visit is conducted in person, obtain a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age), unless advised otherwise by Pfizer.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including
        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg).
        - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg or requiring vasopressors).
        - Significant acute renal, hepatic, or neurologic dysfunction.

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).

  - Clinical diagnosis.

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

  - Full blood count.

  - Blood chemistry, specifically creatinine, urea, LFTs, and CRP.

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction.

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay.

  - Death.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

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

This visit is to be completed 28 to 35 days after all potential COVID-19 illness visits. A separate blood sample is needed for this visit for testing purposes even if it coincides with another scheduled visit.

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.10.8).

- Record details of any of the prohibited medications specified in Section 6.9.1 received by the participant if required for his or her clinical care.

- Record AEs as described in Section 8.4. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment only on the relevant pages of the CRF, as these are expected endpoints.

- Collect a blood sample (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants 12 through 17 years of age), unless advised otherwise by Pfizer.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.10. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 1: To determine whether a participant will be included in efficacy analyses of those with no evidence of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the vaccination visit swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant or participant's parent(s)/legal guardian should be directed to seek additional testing through the participant's primary healthcare provider at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing, as per local guidance.

8.10.11. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after the study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis. In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

8.10.12. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in the SAP, which will be maintained by Pfizer. 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. Statistical Hypothesis

Cohort 1 and Cohort 2: For objectives evaluated separately within Cohort 1 and Cohort 2, there is no formal hypothesis testing. All statistical analyses will be descriptive.

Cohort 2 + Cohort 3 combined:

Superiority and Noninferiority of Anti-Omicron Immune Responses

For the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):

The primary immunogenicity objective is to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group relative to the anti-Omicron immune response elicited by BNT162b2 30 µg in the >55-age group from C4591031 Substudy E. The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(1) corresponds to a 1-fold margin for superiority and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 in the >55-age group from C4591031 Substudy E.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } H_1: p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - p_2 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 in the >55-age group from C4591031 Substudy E.

Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Superiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

For the 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined):

The primary immunogenicity objective is to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1) relative to the anti-Omicron immune response elicited by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2). The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1);

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2).

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.1 \text{ vs } H_1: p_1 - p_2 > -0.1$$

where -10% is the noninferiority margin for seroresponse and

  - p_1 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1)

- p_2 Is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2).

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Noninferiority of Anti–Reference-Strain Immune Responses

The secondary immunogenicity objective is to assess the noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group relative to the anti–reference-strain immune response elicited by BNT162b2 30 µg in the >55-age groups. The noninferiority objective will be evaluated by the following hypothesis:

- The null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

- Ln(μ_1) is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2);

- Ln(μ_2) is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 in the >55-age group from C4591031 Substudy E.

Noninferiority based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in Section 3.

The primary safety objective evaluations are based on the safety population. In general, completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially missing reactogenicity e-diary data (eg, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days. Missing AE start 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 the evaluable immunogenicity population (Section 9.2). 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.

9.1.2. Multiplicity Adjustment

Cohort 1 and Cohort 2: No multiplicity adjustment is needed for objectives evaluated separately within Cohort 1 and Cohort 2 as there are no statistical hypotheses.

Cohort 2 + Cohort 3 combined:

The primary and secondary objectives will be evaluated sequentially using a 1-sided alpha of 0.025. The primary objective for the >55-age group will be evaluated first, followed by the secondary objective of the GMR for >55-age group, and then the primary objective for the 18- through 55-age group. The later objective will be evaluated only if the previous objective is met.

The primary objectives involve 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error is fully controlled.

9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.

Population	Description
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized/assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity (mITT)	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

9.3.1. General Considerations

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population 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.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson). The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.

The primary approach to calculate the difference in seroresponse rate between 2 vaccine groups and the associated 95% CI will be based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median).

9.3.1.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

9.3.1.3. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

Model-Based GMR:

As the primary approach, the GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes terms for baseline neutralizing titer and comparison group.

Unadjusted GMR:

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.4. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points. GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.5. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

9.3.2. Primary Endpoints/Estimands Analysis

Endpoint	Statistical Analysis Methods
Safety	Cohort 1: • Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group. Cohort 2, and Cohort 2 + Cohort 3 combined: • Reactogenicity, AEs, and SAEs will be summarized for each age group and vaccine dose-level group in the same way as described above for Cohort 1.
Immunogenicity	For each primary immunogenicity estimand described in Section 9.3.1, Cohort 1: • GMTs and 2-sided 95% CIs will be provided for each vaccine group at each time point for SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)–neutralizing and reference-strain–neutralizing titers. GMTs will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.3. • GMFRs of SARS-CoV-2 Omicron (sublineages BA.1 and BA.2)–neutralizing and reference-strain–neutralizing titers from baseline (before the study vaccination) to each subsequent time point, along with the associated 2-sided 95% CIs will be provided for each vaccine group. GMFRs will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.4.

Endpoint	Statistical Analysis Methods
	• The percentages of participants with seroresponse to Omicron (sublineages BA.1 and BA.2) and reference strain at each time point after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. The percentages of participants with seroresponse will be summarized in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. • GMTs, GMFRs, and percentages of participants with seroresponse, along with the associated 95% CIs, will also be summarized by baseline SARS-CoV-2 infection status. Cohort 2: • For each age group and vaccine dose-level group included in Cohort 2 and the selected subset of participants in the BNT162b2 (WT/OMI BA.1) 30-µg or 60-µg group from C4591031 Substudy E (≥18 years of age, see Section 4.1 for details), GMTs and GMFRs of SARS-CoV-2 Omicron (sublineages BA.1 and BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (sublineages BA.1 and BA.4/BA.5) and reference strain, along with the associated 95% CIs, will be summarized in the same way as described above for Cohort 1. Cohort 2 + Cohort 3 combined: For each primary immunogenicity objective described in Section 3 for Cohort 2 + Cohort 3 combined, • GMR of SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titer at 1 month after the study vaccination and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.3 in participants with and without evidence of SARS-CoV-2 infection. As the primary approach to calculate the GMR and CI for neutralizing titer, a linear regression model that includes terms for baseline neutralizing titer and comparison group will be used to calculate the GMR and 95% CI, along with the model-based LS GMTs and associated 2-sided 95% CIs for each group. • The percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after the study vaccination will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated

Endpoint	Statistical Analysis Methods
	using the Miettinen and Nurminen method (see Section 9.3.1.1) in participants with and without evidence of SARS-CoV-2 infection. The primary approach to calculate the difference in seroresponse rate between 2 comparison groups and the associated 95% CI will be Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). • For the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined), superiority based on GMR will be established if the model-based lower bound of the 2-sided 95% CI for GMR is greater than 1. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -5%. • For the 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined), noninferiority based on GMR will be established if the model-based lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -10%.

9.3.3. Secondary Endpoints

Endpoint	Statistical Analysis Methods
Immunogenicity	For each secondary immunogenicity estimand described in Section 3 for Cohort 2 + Cohort 3 combined: • GMR of the SARS-CoV-2 reference-strain–neutralizing titer at 1 month after the study vaccination and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.3 in participants with and without evidence of SARS-CoV-2 infection. A linear regression model that includes terms for baseline neutralizing titer and comparison group will be used to calculate the GMR and 95% CI, along with the model-based LS GMTs and associated 2-sided 95% CIs for each comparison group. • Noninferiority will be established if the model-based lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8. • GMTs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers and 2-sided 95% CIs will be provided for each age group at each time point. GMTs

Endpoint	Statistical Analysis Methods
	will be summarized in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.3. • GMFRs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers from baseline (pre–Dose 1) to each subsequent time point, along with the associated 2-sided 95% CIs, will be provided for each age group. GMFRs will be summarized in participants with and without evidence of SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.4. • The percentages of participants with seroresponse to Omicron (sublineages BA.4/BA.5)– and reference-strain–neutralizing titers at each time point after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each age group. The percentages of participants with seroresponse will be summarized in participants with and without evidence of SARS-CoV-2 infection. • GMTs, GMFRs, and percentages of participants with seroresponse, along with the associated 95% CIs, will also be summarized by baseline SARS-CoV-2 infection status.

9.3.4. Exploratory Endpoints

Endpoint	Statistical Analysis Methods
COVID-19 cases	Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: • Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized for each vaccine and age group.
Immune response to SARS-CoV-2 infection	Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: • SARS-CoV-2–neutralizing titers at the time of a COVID-19 illness visit* and at the convalescent visit will be listed. (*Only for in-person COVID-19 visits.)

Endpoint	Statistical Analysis Methods
Immune response to emerging VOCs	Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: • GMTs of SARS-CoV-2 VOC–neutralizing titers for VOCs not already specified, along with the associated 2-sided 95% CIs, will be provided at specific time points for each vaccine group. GMFRs from baseline (before the study vaccination) to each subsequent time point, percentage of participants with seroresponse at each time point after vaccination, along with the associated 2-sided 95% CIs, may also be provided for each vaccine group.
Cell-mediated immune response	Cohort 2: • The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron variant will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

9.4. Interim Analyses

As Cohort 1 is a sponsor open-label, Phase 2 study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

No formal interim analysis will be conducted. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 9.4.1.

9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available for each of Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined:

- Safety and immunogenicity data through Visit 3 (1 month after study vaccination).
- Safety and immunogenicity data through Visit 5 (6 months after study vaccination).

Additional analyses may be conducted if required for regulatory purposes.

9.5. Sample Size Determination

Cohorts 1 and 2: For the immunogenicity analyses conducted separately for Cohorts 1 and 2, the sample size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

For safety outcomes, Table 7 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 2%, with 100, 200, or 300 participants in a group, there is 87%, 98%, and >99% probability of observing at least 1 AE, respectively.

Table 7. Probability of Observing at Least 1 AE by Assumed True Event Rate

Assumed True Event Rate of an AE	N=100	N=200	N=300
0.1%	0.10	0.18	0.26
0.3%	0.26	0.45	0.59
0.5%	0.39	0.63	0.78
0.8%	0.55	0.80	0.91
1%	0.63	0.87	0.95
2%	0.87	0.98	>0.99
3%	0.95	>0.99	>0.99
4%	0.98	>0.99	>0.99
5%	0.99	>0.99	>0.99

Cohort 2 + Cohort 3 combined: To provide sufficient power for the immunogenicity hypotheses for each of the age groups, the Cohort 2 18- through 55-age and >55-age groups receiving a 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) will be combined with the corresponding age and dose groups in Cohort 3.

Superiority and Noninferiority of Anti-Omicron Immunogenicity Objective

- For the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined vs BNT162b2 30-µg group from C4591031 Substudy E):

Assuming a 20% nonevaluable rate, with 300 participants >55 years of age receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg (100 in Cohort 2/Group 2 and 200 in Cohort 3/Group 2) and 300 participants >55 years of age receiving BNT162b2 30 µg (from C4591031 Substudy E), approximately 480 evaluable participants (240 in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and 240 in the BNT162b2 30-µg group) will contribute to the immunogenicity evaluation. The superiority evaluation based on GMR and noninferiority evaluation based on seroresponse rate difference will each be performed at 1-sided alpha level of 0.025 as described in Section 9.1.2.

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose in log scale is assumed to be 1.45 based on data observed in the C4591031 Substudy E. If the true GMR of Omicron–neutralizing titer in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to the BNT162b2 30-µg group is 1.5, then 480 evaluable participants will provide 86.4% power to declare noninferiority.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 65% in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and 52% in the BNT162b2 30-µg group, the study has 98.0% power to demonstrate noninferiority using a 5% margin.

- For the 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined) vs >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):

Assuming a 20% nonevaluable rate, with 300 participants receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-age group (100 in Cohort 2/Group 2 and 200 in Cohort 3/Group 1) and 300 participants receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group (100 in Cohort 2/Group 4 and 200 in Cohort 3/Group 2), approximately 240 evaluable participants in each age group (18- through 55-age group and >55-age group) will contribute to the immunogenicity evaluation. The noninferiority evaluation based on GMR and seroresponse rate difference will each be performed at 1-sided alpha level of 0.025 as described in Section 9.1.2.

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose in log scale is assumed to be 1.45 based on data observed in the C4591031 Substudy E. If the true GMR of Omicron–neutralizing titer after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- through 55-age group to the >55-age group is 1, then 480 evaluable participants (240 in the 18- through 55-age group and 240 in the >55-age group) will provide 86.4% power to declare noninferiority.

For comparisons based on seroresponse rate difference, if the seroresponse rate after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg is 65% in the 18- through 55-age group and 65% in the >55-age group, the study has 63.4% power to demonstrate noninferiority using a 10% margin.

Noninferiority of Anti–Reference-Strain Immunogenicity Objective

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose in log scale is assumed to be 1.05 based on data observed in the C4591031 Substudy E. If the true GMR of reference-strain–neutralizing titer after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg to after BNT162b2 30 µg in the >55-age group is 1, then 480 evaluable participants (240 in the BNT162b2 Bivalent [WT/OMI BA.4/BA.5] 30-µg group and 240 in the BNT162b2 30-µg group) will provide 98.8% power to declare noninferiority using a 1.5-fold margin.

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, 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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide Pfizer with sufficient, accurate financial information as requested to allow Pfizer to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent/Assent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and/or his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and/or his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants must be informed that their participation is voluntary. Participants and/or the participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant and/or his/her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant and/or his/her parent(s)/legal guardian must be informed that the participant's 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 and/or his/her parent(s)/legal guardian.

The participant and/or his/her parent(s)/legal guardian must be informed that the participant's 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 and/or his/her parent(s)/legal guardian is fully informed about their right to access and correct the participant's personal data or their child's personal data and to withdraw consent for the processing of the participant's personal data or their child's personal data.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date on which the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants and/or the participant's parent(s)/legal guardian must be reconsented to the most current version of the IRB/EC-approved ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent(s) must be provided to the participant and/or his/her parent(s)/legal guardian.

Participants who are rescreened are required to sign a new ICD.

10.1.4. 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an EDMC. The EDMC is independent of the study team and includes only external members. The EDMC charter describes the role of the EDMC in more detail.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

10.1.6. 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/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-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 data from these trials available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor's designee.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. 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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 the ICH 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.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and

responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

If appropriate, a pregnancy test will be performed at times defined in the SoA.

- Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for participants who are WOCBP.

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.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
• New condition 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 or 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 that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting 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	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or 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 or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or 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 or SAE.

Assessment of Intensity

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.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting 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 submitted documents.
- 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 an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier 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 as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 agrees to use an acceptable contraceptive method 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 a 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.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she 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.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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 WOCBP 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.

Highly Effective Methods That Are User Dependent

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

    - Oral;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

Sexual Abstinence

8. 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.

Other Effective Methods

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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor or sponsor's designee will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.6) will be stored for up to 15 years or other period as per local requirements.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: 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 "adaptors" 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 T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 Pfizer.

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 T bili for suspected Hy's law cases, 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, or 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, 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 T bili 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.

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr (*mg/dL*)**	**Scys (*mg/L*)**	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr (*mg/dL*)**	**Scys (*mg/L*)**	**Recommended eGFR Equation**
Female	If ≤ 0.7	If ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	If ≤ 0.7	If > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	If > 0.7	If ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	If > 0.7	If > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	If ≤ 0.9	If ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	If ≤ 0.9	If > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	If > 0.9	If ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	If > 0.9	If > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

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10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE/KDIGO criteria.

10.8. Appendix 8: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (27 Jul 2022)

Overall Rationale for the Amendment:

Inclusion of a second cohort to describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg in individuals ≥12 years of age and at 60 µg in adults ≥18 years of age. Added corresponding objectives, estimands, and endpoints and details in the statistical methods sections. Study intervention details and background information supporting inclusion of this cohort were added.

Inclusion of prospective capture of confirmed COVID-19 cases for both Cohorts 1 and 2 with active COVID-19 surveillance and convalescent visits.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis	Updated the text with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in participants 12 years of age and above and 60 µg in participants 18 years of age and above.	Substantial
Section 1.2 Schema	Added Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 1.3 Schedule of Activities	Added text to include PBMC and HLA sampling in Cohort 2. Added blood volume for participants 12 through 17 years of age. Added reminder to obtain assent for pediatric population.	To describe B-cell and T-cell responses to Omicron and the reference strain. To accommodate reduced blood draw volume for the younger age group. To reflect changed informed consent process for pediatric population of Cohort 2.	Substantial
Section 2 Introduction	Added text to provide background on the emergence of additional Omicron sublineages; added rationale for the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 3 Objectives, Endpoints, and Estimands	Updated the text with respect to the addition of Cohort 2.	To describe the analysis of data from Cohort 2.	Substantial
Section 4 Study Design	Updated the text with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 5.1 Inclusion Criteria	Updated inclusion criteria 1, 2, 4, and 5 with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 6 Study Intervention(s) and Concomitant Therapy	Updated the text with respect to the addition of Cohort 2.	To obtain data on BNT162b2 Bivalent (WT/OMI BA.4/BA.5).	Substantial
Section 6.4 Blinding	Updated the text with respect to the addition of Cohort 2.	To describe the change in blinding for Cohort 2.	Substantial
Section 8 Study Procedures	Added text to include PBMC and HLA sampling in Cohort 2. Added text regarding the total blood sampling volume for participants providing these optional samples. Added text regarding the total blood sampling volume for participants 12 through 17 years of age.	To describe B-cell and T-cell responses to Omicron and the reference strain. To accommodate reduced blood draw volume for the younger age group.	Substantial
Section 9.3.4 Exploratory Objectives	Updated the text with respect to the addition of Cohort 2.	To describe the analysis of data from Cohort 2	Substantial
Section 10.5 Genetics	Added Section 10.5 because of the inclusion of PBMC sampling in Cohort 2.	To describe B-cell and T-cell responses to Omicron and the reference strain.	Substantial
Section 1.1 Synopsis	Updated the exploratory objectives and endpoints to include confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group, with respect to COVID-19 surveillance.	To describe the analysis of data from COVID-19 surveillance.	Substantial
Section 1.2 Schema	Added COVID-19 Surveillance.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3 Schedule of Activities	Added text with respect to COVID-19 surveillance and activities related to potential COVID-19 illness visits and convalescent visits. This includes provision of nasal self-swab kits and instructions on self-collection of nasal swabs. Included statement that any AEs occurring within 48 hours of nasal swab collection should be reported. Because of inclusion of the illness e-diary, deletion of the e-diary application or collection of the provisioned device was moved from the 1-month follow-up visit to the 6-month follow-up visit.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial
Section 3 Objectives, Endpoints, and Estimands	Updated the exploratory objectives and endpoints to include confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group, with respect to COVID-19 surveillance.	To describe the analysis of data from COVID-19 surveillance.	Substantial
Section 4.2 Scientific Rationale	Updated the text with respect to COVID-19 surveillance.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial
Section 8 Study Procedures	Updated the text with respect to COVID-19 surveillance and procedures related to potential COVID-19 illness visits and convalescent visits. Because of inclusion of the illness e-diary, deletion of the e-diary application or collection of the provisioned device was removed from the 1-week and 1-month follow-up visits to the 6-month follow-up visit.	To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.	Substantial
Section 8.4.8 Adverse Events of Special Interest	Updated to remove confirmed COVID-19 diagnosis as an AESI.	To include COVID-19 illness visits. To capture COVID-19 within that data set and not to duplicate it as an AE.	Substantial
Section 9.3.4 Exploratory Endpoints	Updated with respect to exploratory objective and endpoints for COVID-19 surveillance.	To describe the analysis of data from COVID-19 surveillance.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3 Schedule of Activities	Removed allowance for Visit 1 to be conducted over 2 consecutive days.	To align with recruitment expectations and visit scheduling.	Nonsubstantial
Section 4.2.2 Choice of Contraception/Barrier Requirements	Updated the text with respect to the addition of Cohort 2.	To clarify the requirement for contraception.	Nonsubstantial
Section 5.5 Temporary Delay Criteria	Replaced "oral temperature" with "body temperature." The temperature measurement route is per investigator discretion.	To align with Sections 1.3 (Schedule of Activities), 8.3.2 (Vital Signs), and 8.10.1 (Visit 1 study procedures).	Nonsubstantial
Section 6.3 Assignment to Study Intervention	Added day range to strata.	To clarify stratification.	Nonsubstantial
Section 8.10.1 Visit 1 – Study Intervention Administration – Day 1	Removed the allowance for Visit 1 to be conducted over 2 consecutive days.	To align with recruitment expectations and visit scheduling.	Nonsubstantial
All	Administrative corrections to formatting, typographical errors, and naming of "Pfizer," where necessary.	Administrative correction.	Nonsubstantial
Section 11 References	Updated with respect to text added per protocol amendment 1 changes.	To record additional references.	Nonsubstantial

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BCR	B-cell receptor
β-hCG	β-human chorionic gonadotropin
BNP	brain natriuretic peptide
BNT162b2 Bivalent (WT/OMI BA.1)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.1)
BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529 sublineage BA.2)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
ChAdOx1-S	ChAdOx1-S (recombinant) SARS-CoV-2 vaccine (AstraZeneca)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DCT	data collection tool
DILI	drug-induced liver injury

Abbreviation	Term
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	emergency use authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification

Abbreviation	Term
IgG	immunoglobulin G
IL-6	interleukin-6
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
KDIGO	Kidney Disease: Improving Global Outcomes
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LS	least square
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MQI	medically qualified individual
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-1273 SARS-CoV-2 vaccine (Moderna)
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NIMP	noninvestigational medicinal product
OMI	Omicron
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
P6’ S	SARS-CoV-2 full-length, P6 prime mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve

Abbreviation	Term
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
TCR	T-cell receptor
Th1	T-helper type 1
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vax	vaccination
VE	vaccine efficacy
VOC	variant of concern
WOCBP	woman/women of childbearing potential
WT	wild type

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Protocol C4591044

AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2 OBSERVER-BLIND STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BIVALENT BNT162b RNA-BASED VACCINE CANDIDATE AS A BOOSTER DOSE IN COVID-19 VACCINE–EXPERIENCED HEALTHY ADULTS

Statistical Analysis Plan
(SAP)

Version: 1

Date: 12 Jul 2022

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol	Rationale	Specific Changes
1 12 Jul 2022	Original 24 Jun 2022	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591044. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary and exploratory objectives are described in Table 2 below.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules (Section 5.2). In general, completely missing reactogenicity data (ie, all 7 days of e-diary collection were missing and no reactogenicity data were reported as AEs) will not be imputed. For the partially missed reactogenicity data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (see Section 4 for definition). 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.

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Safety		
To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Primary Immunogenicity		
To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)-neutralizing titers • SARS-CoV-2 Omicron (BA.1)-neutralizing titers • SARS-CoV-2[b]-strain–neutralizing titers
Exploratory		
To describe the immune response to emerging VOCs		• SARS-CoV-2–neutralizing titers for Omicron sublineages and VOCs not already specified

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. Reference strain is also referred to as the Wild Type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).

2.3. Study Design

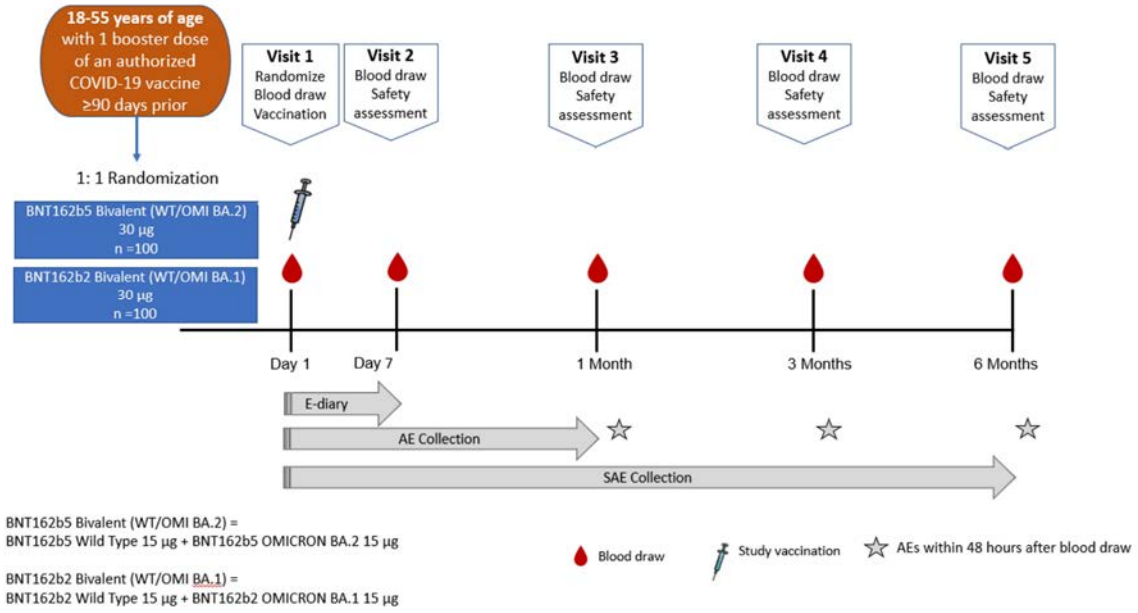
This study is a randomized, active-controlled, observer-blinded study to evaluate a new bivalent vaccine at a total dose level of 30 µg. The study will evaluate safety, tolerability and immunogenicity. The study duration for each participant will be approximately 6 months. Refer to the Schema in Figure 1.

Participants will be randomized at a ratio of 1:1 to receive a single dose of BNT162b5 Bivalent (WT/OMI BA.2) or BNT162b2 Bivalent (WT/OMI BA.1). Participants will be stratified by the number of months since the last dose of COVID-19 vaccine received prior to entering the study (3 to 6 months or >6 months).

Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed, and study visits or other procedures may be discontinued.

An external EDMC will review cumulative unblinded data throughout the study.

Figure 1. Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Safety Endpoints

The primary safety endpoints are as follows:

- Local reactions for up to 7 days after the study vaccination
- Systemic events for up to 7 days after the study vaccination
- AEs from vaccination through 1 month after the study vaccination
- SAEs from vaccination through 6 months after the study vaccination

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after the study vaccination, where Day 1 is the day of the study vaccination. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 3 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of the study vaccination.

Table 3. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for the Study Vaccination

Variable	Yes (1)	No (0)
Presence of each local reaction on any day.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).
Presence of any local reaction on any day.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).

Note: Completely missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4. 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 4.

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the CRF and assessed by the investigator using the AE intensity grading scale.

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 Pfizer.

For each local reaction reported after the study vaccination, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of the study vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after administration (Day 1 through Day 7) among severity grades reported for that local reaction in the e-diary.

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive (last day of reaction − first day of reaction + 1). Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasts 7 days or less, or the day the reaction ends if it persists beyond the end of the reactogenicity e-diary period following the study vaccination (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if participants report change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after the study vaccination. The derivations for systemic events will be handled similar to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

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.

Table 5. 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

Table 5. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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.

During the 7 days following the study vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if a positive test result, the symptoms should be recorded as an AE of COVID-19 rather than as systemic events in the reactogenicity e-diary. Such COVID-19 diagnoses should be reported as AEs as per the protocol, Section 8.4. AEs of confirmed COVID-19 are considered to be AEs of special interest (refer to the protocol, Section 8.4.8).

Temperature will be collected in the evening, daily, for 7 days following the study vaccination (Days 1 through 7, where Day 1 is the day of the study vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 6 below.

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 Pfizer. Fevers >40.0°C (>104.0°F) will be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (protocol, Section 10.3.3).

Table 6. 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)

3.1.1.3. Antipyretic/Analgesic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of the study vaccination. For the use of antipyretic medication from Day 1 through Day 7 after the study vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7)
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7)
- Duration (first to last day reported) of use of antipyretic medication
- Onset day of use of antipyretic medication

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after the study vaccination. In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF. AEs will be categorized according to MedDRA terms. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.2.

The primary safety endpoint "AEs from the study vaccination through 1 month after the study vaccination" and other AE endpoints will be summarized by SOC and PT.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol).

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent through approximately 6 months after the study vaccination. SAEs will be categorized according to MedDRA terms. The primary safety endpoint "SAEs from vaccination through 6 months after the study vaccination" will be summarized by SOC and PT at the participant level for each vaccine group. Additionally, SAEs will be listed.

3.1.2. Primary Immunogenicity Endpoints

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- SARS-CoV-2 Omicron (BA.2)–neutralizing titers at each time point
- SARS-CoV-2 Omicron (BA.1)–neutralizing titers at each time point
- SARS-CoV-2 reference-strain–neutralizing titers at each time point

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Exploratory Endpoint(s)

SARS-CoV-2–neutralizing titers for Omicron sublineages and VOCs not already specified at each time point.

3.4. Baseline Variables

Measurements or samples collected prior to the study vaccination are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables will be collected including date of birth, sex (male or female), race (Black or African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, unknown, and not reported), ethnicity (Hispanic/Latino or of Spanish origin, non-Hispanic/non-Latino or not of Spanish origin, and not reported), and BMI. In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the time of the study vaccination (in years) will be derived based on the participant's birthday. For example, if the study vaccination day is 1 day before the participant's 20^{th} birthday, the participant is considered to be 19 years old.

Medical history will be collected and categorized according to the current version (at the time of reporting) of MedDRA.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

3.4.2. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all the items on the e-diary for all 7 days after vaccination, the e-diary will be considered not transmitted.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Prohibited medications listed in the protocol, Section 6.9.1, will be recorded in the concomitant medication CRF to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.
- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.
- Prior and concomitant vaccines and concomitant medications will be coded using the WHO Drug Dictionary.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the Primary Safety Endpoints section (Section 3.1.1).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in the table below. Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.

Population	Description
Evaluable immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have at least 1 valid and determinate immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity (mITT)	All randomized participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

Important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those participants with important protocol deviations that result in exclusion from analysis populations.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. In general, completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially missed reactogenicity e-diary data (eg, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. 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.

There is no formal hypothesis testing. All statistical analyses will be descriptive.

The majority of Pfizer staff will be unblinded to the study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to the study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 6.4. The timing for statistical analysis is specified in Section 7.3.

5.1. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

5.1.1. Analyses for Binary Endpoints

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs, where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

5.1.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.1.3. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

5.1.4. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.1.5. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

5.2. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the study vaccination date(s) from the same participant, following the Pfizer standard for handling an incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

Missing serology 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.1.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For the partially missed reactogenicity e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days. Confirmed e-diary errors will be excluded from the analysis.
- Reporting results: Descriptive statistics for each and any local reaction after the study vaccination in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Suppliemental Analysis

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population as above, and appropriate analysis methodology and reporting results:

- Duration (days) of each local reaction after the study vaccination.
- Onset day of each local reaction after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by vaccine group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after the study vaccination will be plotted by vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimands: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.1.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For the partially missed reactogenicity e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced. Confirmed e-diary errors will be excluded from the analysis.
- Reporting results: Descriptive statistics for each systemic event after the study vaccination in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analysis

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after the study vaccination.
- Onset day of each systemic event after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by vaccine group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the study vaccination through 1 month after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 1 month after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.1.1 and Section 3.1.1.4).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.2).
- Reporting results: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of AEs within 1 month after the study vaccination will be provided for each vaccine group.

6.1.1.3.2. Supplemental Analysis

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol) will also be summarized by vaccine group.

All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be in the listing.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from the study vaccination through 6 months after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 6 months after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.1.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.2).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the study vaccination through 6 months after the study vaccination will be provided for each vaccine group.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Main Analysis

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- Estimands:
  - GMTs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers at each timepoint for each vaccine group
  - GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers from before the study vaccination to subsequent time points for each vaccine group
  - Percentages of participants with seroresponse to Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers at each time point
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.1.3. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.1.4. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group (Section 5.1.1).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers from baseline (before the study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group for participants without evidence of SARS-CoV-2 infection and for participants with and without evidence of SARS-CoV-2 infection. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group for participants without evidence of SARS-CoV-2 infection and for participants with and without evidence of SARS-CoV-2 infection. Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post vaccination measure of ≥4 × LLOQ is considered seroresponse.

6.2. Exploratory Endpoint(s)

6.2.1. SARS-Cov-2 VOC-Neutralizing Titers For Omicron Sublineages and VOCs Not Already Specified

6.2.1.1. Main Analysis

- Estimands:
    - GMTs of SARS-CoV-2 VOC-neutralizing titers for Omicron sublineages and VOCs not already specified at specific timepoint for each vaccine group
    - GMFRs of SARS-CoV-2 VOC-neutralizing titers for Omicron sublineages and VOCs not already specified from before the study vaccination to subsequent time points for each vaccine group
    - Percentages of participants with seroresponse to SARS-CoV-2 VOC–neutralizing titers for Omicron sublineages and VOCs not already specified at each time point
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.1.3. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.1.4. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group (Section 5.1.1).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2–neutralizing titers for Omicron sublineages and VOCs from baseline (before the study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post vaccination measure of ≥4 × LLOQ is considered seroresponse.

6.3. Subset Analyses

Subgroup analyses based on sex, the number of months since the last dose of the COVID-19 vaccine received prior to entering the study (3-6 months or >6 months), and baseline SARS-CoV-2 status will be performed on all immunogenicity endpoints as supplemental analyses and for all primary safety endpoints (for sex subgroup only).

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

6.4.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination, sex, race, ethnicity, baseline SARS-CoV-2 status, and classification of BMI, will be summarized using descriptive statistics for each vaccine group based on the safety population and the evaluable immunogenicity population. Timing and name of all previous doses of COVID-19 Vaccinations prior to enrollment will also be summarized for each vaccine group.

6.4.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of participants with at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group for the safety population.

6.4.2. Study Conduct and Participant Disposition

6.4.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the disposition summary. In addition, the numbers and percentages of participants who received the study vaccination, who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately along with the reasons for exclusion, by vaccine group.

6.4.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for each time point by vaccine group.

6.4.2.3. Transmission of E-Diaries

The number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for the study vaccination will be summarized according to the vaccine actually received.

The safety population will be used.

6.4.3. Study Intervention Exposure

6.4.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving the study intervention will be tabulated, for each vaccine group and overall, for all randomized participants. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall.

A listing of participants showing the randomized vaccine and the vaccine actually received at the study vaccination will be presented.

6.4.3.2. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before the study vaccination will be listed. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated by vaccine group. Prohibited medications will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications will be provided. The safety population will be used.

6.5. Safety Summaries and Analyses

6.5.1. Adverse Events

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in the Primary Safety Endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below. As this is a sponsor open-label Phase 2 study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analyses Timing

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

- Safety and immunogenicity data through Visit 3 (1 month after study vaccination).
- Safety and immunogenicity data through Visit 5 (6 months after study vaccination).

Certain analyses may be combined as one regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes.

8. REFERENCES

1. Collett D. Statistical inference for binary data. Chapter 2. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
BNT162b2 Bivalent (WT/OMI BA.1)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.1)
BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529 sublineage BA.2)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
EDMC	external data monitoring committee
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IRT	interactive response technology
IRC	internal review committee
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
OMI	Omicron
PT	preferred term
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
VOC	variant of concern
WHO	World Health Organization
WT	wild type

Protocol C4591044

AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2/3 STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BIVALENT BNT162b RNA-BASED VACCINE CANDIDATE AS A BOOSTER DOSE IN COVID-19 VACCINE–EXPERIENCED HEALTHY INDIVIDUALS

Statistical Analysis Plan
(SAP)

Version: 3

Date: 14 Nov 2022

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol	Rationale	Specific Changes
1 12 Jul 2022	Original 24 Jun 2022	N/A	N/A
2 15 Sep 2022	Protocol amendment 1 (PA1), 27 Jul 2022 Protocol amendment 2 (PA2), 24 Aug 2022	1. Adjusted the study design to include pediatric participants; removed the blinding level and changed Phase 2 to Phase 2/3 2. Added primary safety and immunogenicity objectives, endpoints, and estimands for each cohort 3. Added secondary objectives, endpoints, and estimands 4. Added exploratory objectives, endpoints, and estimands for each cohort. 5. Changed the reporting of COVID-19 symptoms in the event of a positive COVID-19 test result. Included information about participants taking medications intended to treat COVID-19 6. Made adjustments to the general statistical methods 7. Adjusted analyses timing in accordance with regulatory agency's feedback 8. Deleted "vaccine" when in front of "group;" added "assigned" with "randomized"; removed "Omicron sublineages"	1. Changed the title, Section 2.3, Section 3.1.1.5, Section 7, and Figure 1. 2. Changed Section 2.2, Section 3.1.1, Section 3.1.2, Section 6.1.1, and Section 6.1.2 3. Changed Section 2.2 and Section 3.2; added Section 6.2 4. Changed Section 2.2, Section 3.3, and Section 6.3 5. Changed Section 3.1.1.2 and Section 3.4.3 6. Added Section 5.1 and Section 5.2.4; changed Section 5.2.1 7. Changed Section 7.3 8. Changed throughout the document
3 14 Nov 2022	Protocol amendment 2 (PA2), 24 Aug 2022	Per CBER's request, clarified the method of calculating the median baseline titer level for the analysis of the differences in seroresponse rates using the Miettinen and Nurminen method stratified by the baseline titer category (< median or ≥ median)	Changed Section 5.2.1 and Section 6.1.2.2.1

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591044. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objectives are described in Table 2 below.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules (Section 5.3). In general, completely missing reactogenicity data (ie, all 7 days of e-diary collection were missing and no reactogenicity data were reported as AEs) will not be imputed. For the partially missed reactogenicity data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (see Section 4 for definition). 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.

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)-neutralizing titers 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)-neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18-55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18-55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[d] or 60 µg[d] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55[d], and >55[d] years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Exploratory		
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[e] and at the convalescent visit		• SARS-CoV-2–neutralizing titers previously specified for the respective cohorts

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to emerging VOCs		• SARS-CoV-2–neutralizing titers for VOCs not already specified
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[b] and Omicron in a subset of participants with PBMC samples collected		

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. Reference strain is also referred to as the Wild Type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
c. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
d. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received Bivalent BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.
e. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

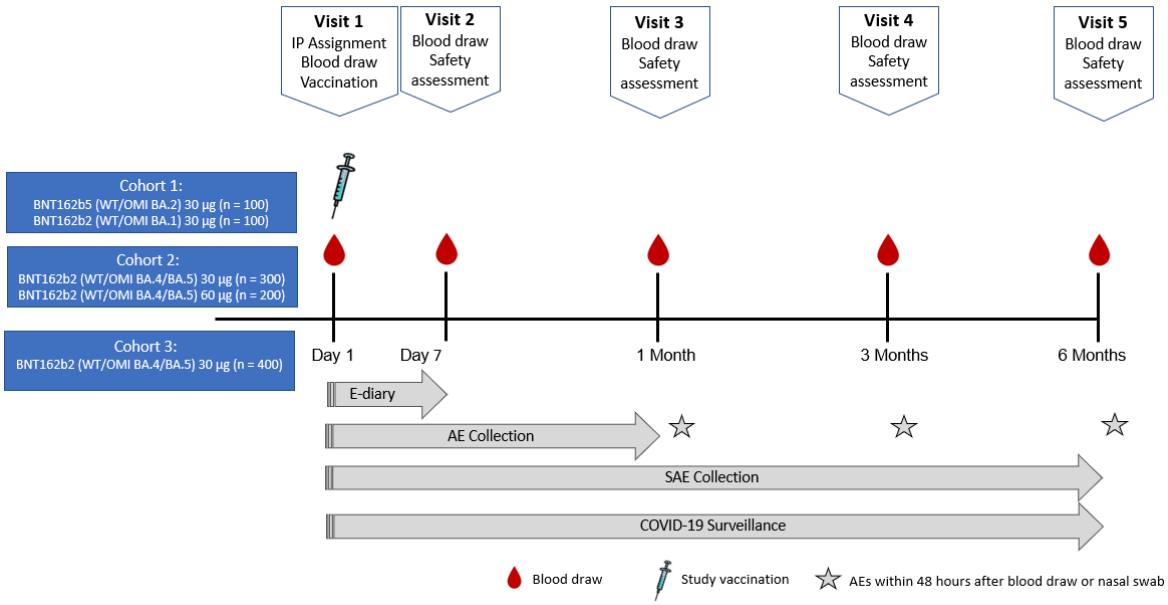
2.3. Study Design

This study is a randomized, active-controlled, study to evaluate the safety, tolerability, and immunogenicity of new bivalent vaccines. The study duration for each participant will be approximately 6 months. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan. Refer to the Schema in Figure 1.

Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed, and study visits or other procedures may be discontinued.

An EDMC will review cumulative unblinded data throughout the study.

Figure 1. Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Safety Endpoints

The primary safety endpoints for all analysis groups are as follows:

- Local reactions for up to 7 days after the study vaccination
- Systemic events for up to 7 days after the study vaccination
- AEs from vaccination through 1 month after the study vaccination
- SAEs from vaccination through 6 months after the study vaccination

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after the study vaccination, where Day 1 is the day of the study vaccination. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 3 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of the study vaccination.

Table 3. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for the Study Vaccination

Variable	Yes (1)	No (0)
Presence of each local reaction on any day.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).
Presence of any local reaction on any day.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).

Note: Completely missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4. 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 4.

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the CRF and assessed by the investigator using the AE intensity grading scale.

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 Pfizer.

For each local reaction reported after the study vaccination, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of the study vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after administration (Day 1 through Day 7) among severity grades reported for that local reaction.

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive (last day of reaction − first day of reaction + 1). Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasts 7 days or less, or the day the reaction ends if it persists beyond the end of the reactogenicity e-diary period following the study vaccination (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if participants report change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after the study vaccination. The derivations for systemic events will be handled similar to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

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.

Table 5. 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

Table 5. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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.

During the 7 days following the study vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if a positive test result, the symptoms should be recorded in the potential COVID-19 illness CRFs (with potential COVID-19 illness visit completed) rather than as systemic events in the reactogenicity e-diary (refer to the protocol, Sections 8.10.7 and 8.10.8).

Temperature will be collected in the evening, daily, for 7 days following the study vaccination (Days 1 through 7, where Day 1 is the day of the study vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 6 below.

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 Pfizer. Fevers >40.0°C (>104.0°F) will be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (Protocol, Section 10.3.3).

Table 6. 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)

3.1.1.3. Antipyretic/Analgesic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of the study vaccination. For the use of antipyretic medication from Day 1 through Day 7 after the study vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7)
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7)
- Duration (first to last day reported) of use of antipyretic medication
- Onset day of use of antipyretic medication

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after the study vaccination. In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF. AEs will be categorized according to MedDRA terms. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

The primary safety endpoint "AEs from the study vaccination through 1 month after the study vaccination" and other AE endpoints will be summarized by SOC and PT.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol).

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant or participant's parent(s)/legal guardian provides informed consent through approximately 6 months after the study vaccination. SAEs will be categorized according to MedDRA terms. The primary safety endpoint "SAEs from vaccination through 6 months after the study vaccination" will be summarized, by SOC and PT, at the participant level for each group. Additionally, SAEs will be listed.

3.1.2. Primary Immunogenicity Endpoints

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

Cohort 1:

- SARS-CoV-2 Omicron (BA.2)–neutralizing titers at each time point
- SARS-CoV-2 Omicron (BA.1)–neutralizing titers at each time point
- SARS-CoV-2 reference-strain–neutralizing titers at each time point

Cohort 2:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at each time point
- SARS-CoV-2 Omicron (BA.1)–neutralizing titers at each time point
- SARS-CoV-2 reference-strain–neutralizing titers at each time point

Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined:

In participants with and without evidence of SARS-CoV-2 infection:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at 1 month time point

3.2. Secondary Endpoint(s)

For Cohort 2/Group 4 + Cohort 3/Group 2 combined (>55-year age group):

In participants with and without evidence of SARS-CoV-2 infection:

- SARS-CoV-2 reference-strain–neutralizing titers at 1 month time point

For Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined:

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at each time point
- SARS-CoV-2 reference-strain–neutralizing titers at each time point

3.3. Exploratory Endpoint(s)

For Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined:

- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- SARS-CoV-2–neutralizing titers previously specified for the respective cohorts at the COVID-19 illness visit and the convalescent visit
- SARS-CoV-2–neutralizing titers for VOCs not already specified at each time point

For Cohort 2:

- Cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group.

3.4. Baseline Variables

Measurements or samples collected prior to the study vaccination are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables will be collected including date of birth, sex (male or female), race (Black or African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, unknown, and not reported), ethnicity (Hispanic/Latino or of Spanish origin, non-Hispanic/non-Latino or not of Spanish origin, and not reported), and BMI. In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the time of the study vaccination (in years) will be derived based on the participant's birthday. For example, if the study vaccination day is 1 day before the participant's 20th birthday, the participant is considered to be 19 years old.

Medical history will be collected and categorized according to the current version (at the time of reporting) of MedDRA.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

3.4.2. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all the items on the e-diary for all 7 days after vaccination, the e-diary will be considered not transmitted.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Prohibited medications listed in the protocol, Section 6.9.1, will be recorded in the concomitant medication CRF to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.
- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.

- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

- Prior and concomitant vaccines and concomitant medications will be coded using the WHO Drug Dictionary.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the Primary Safety Endpoints section (Section 3.1.1).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in the table below. Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized/assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity (mITT)	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

Important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those participants with important protocol deviations that result in exclusion from analysis populations.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. In general, completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially missed reactogenicity e-diary data (eg, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% 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/assigned. Missing serology data will not be imputed.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. 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.

Cohort 1 and Cohort 2: To facilitate rapid review of data in real time, the majority of Pfizer/BioNTech staff will be unblinded to the study intervention allocation.

Cohort 3: Given the single study intervention arm, both groups are unblinded to the majority of Pfizer staff involved in the conduct of the study.

All Cohorts: All laboratory testing personnel performing serology assays will remain blinded to the study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 6.4. The timing for statistical analysis is specified in Section 7.3.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

Cohort 1 and Cohort 2: For objectives evaluated separately within Cohort 1 and Cohort 2, there is no formal hypothesis testing. All statistical analyses will be descriptive.

Cohort 2 and Cohort 3 combined:

Superiority and Noninferiority of Anti-Omicron Immune Responses

For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):

The primary immunogenicity objective is to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti-Omicron immune response elicited by BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E.

The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(1) corresponds to a 1-fold margin for superiority and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 given as a second booster dose in the >55-year age group from C4591031 Substudy E.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } H_1: p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - p_2 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 given as a second booster dose in the >55-year age group from C4591031 Substudy E.

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Superiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

<u>For the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined)</u>**:**

The primary immunogenicity objective is to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1) relative to the anti-Omicron immune response elicited by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2). The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1);

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2).

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.1 \text{ vs } H_1: p_1 - p_2 > -0.1$$

where -10% is the noninferiority margin for seroresponse and

- p_1 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the 18- to 55-year age group (Cohort 2/Group 2+ Cohort 3/Group 1);

- p_2 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2).

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Noninferiority of Anti–Reference-Strain Immune Responses

The secondary immunogenicity objective is to assess the noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti–reference strain immune response elicited by BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E. The noninferiority objective will be evaluated by the following hypothesis:

- The null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

- $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

- $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 given as a second booster dose in the >55-year age group from C4591031 Substudy E.

Noninferiority based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

5.1.2. Multiplicity Adjustment

Cohort 1 and Cohort 2: No multiplicity adjustment is needed for objectives evaluated separately within Cohort 1 and Cohort 2 as there are no statistical hypotheses.

Cohort 2 + Cohort 3 combined:

The primary and secondary objectives will be evaluated sequentially using a 1-sided alpha of 0.025. The primary objective for the >55-year age group (with respect to the anti-Omicron BA.4/BA.5 immune response) will be evaluated first, followed by the secondary objective of the GMR for the >55-year age group (with respect to the anti–reference-strain immune response), and then the primary objective for the 18- to 55-year age group (with respect to the anti-Omicron BA.4/BA.5 immune response). The later objective will be evaluated only if the previous objective is met.

The primary objectives involve 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error is fully controlled.

5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs, where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

The primary approach to calculate the difference in seroresponse rate between 2 groups and the associated 95% CI will be based on Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers will be calculated based on the pooled data in 2 comparator groups.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.3. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results,

calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

5.2.4. Geometric Means Ratio

Model-Based GMR:

As the primary approach, the GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes terms for baseline neutralizing titer and comparison group.

Unadjusted GMR:

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.5. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean.
The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.6. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values.
Data points will be joined by a step function with data points on the left side of the step.

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the study vaccination date(s) from the same participant, following the Pfizer standard for handling an incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

Missing serology 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoints

All primary safety endpoints will be summarized by age group (as applicable) and vaccine group for Cohort 1, Cohort 2, and Cohort 2 and Cohort 3 combined (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined).

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For the partially missed reactogenicity e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.
- Reporting results: Descriptive statistics for each and any local reaction after the study vaccination in each group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplemental Analysis

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population as above, and appropriate analysis methodology and reporting results:

- Duration (days) of each local reaction after the study vaccination.
- Onset day of each local reaction after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after the study vaccination will be plotted by group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimands: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; completely missing reactogenicity e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For the partially missed reactogenicity e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced.
- Reporting results: Descriptive statistics for each systemic event after the study vaccination in each group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analysis

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after the study vaccination.
- Onset day of each systemic event after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days will be plotted for each group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the study vaccination through 1 month after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 1 month after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1 and Section 3.1.1.4).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of AEs within 1 month after the study vaccination will be provided for each group.

6.1.1.3.2. Supplemental Analysis

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol) will also be summarized by group.

All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be in the listing.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from the study vaccination through 6 months after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 6 months after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).

- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the study vaccination through 6 months after the study vaccination will be provided for each group.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Cohort 1 and Cohort 2

6.1.2.1.1. Main Analysis

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- Estimands (Cohort 1):
    - GMTs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers at each timepoint for each vaccine group
    - GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers from before the study vaccination to subsequent time points for each vaccine group
    - Percentages of participants with seroresponse to Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers at each time point
- Estimands (Cohort 2):
    - GMTs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.4/BA.5) and reference-strain–neutralizing titers at each timepoint for each group (Cohort 2/Group 1 to Group 5 and comparator groups from C4591031 Substudy E, Table 7)
    - GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to subsequent time points for each group (Cohort 2/Group 1 to Group 5 and comparator groups from C4591031 Substudy E, Table 7)
    - Percentages of participants with seroresponse to Omicron strain (sublineages BA.1 and BA.4/BA.5) and reference-strain–neutralizing titers at each time point for each group (Cohort 2/Group 1 to Group 5 and comparator groups from C4591031 Substudy E, Table 7)
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.2.3. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.2.5. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group (Section 5.2.1). Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post vaccination measure of ≥4 × LLOQ is considered seroresponse.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2 for Cohort 1; sublineages BA.1, BA.4/BA.5 for Cohort 2) and reference-strain–neutralizing titers from baseline (before the study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each group for participants without evidence of SARS-CoV-2 infection and for participants with and without evidence of SARS-CoV-2 infection. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group for participants without evidence of SARS-CoV-2 infection and for participants with and without evidence of SARS-CoV-2 infection.

Table 7. Outline of Primary Objectives Groups (Cohort 2)

	C4591044 Cohort 2	C4591031 Substudy E
Study Intervention	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	Bivalent BNT162b2 (WT/OMI BA.1)
Group	Group 1	
Age	12-17	
Dosage level	30 µg	
Group	Group 2	Group 8
Age	18-55	18-55
Dosage level	30 µg	30 µg
Group	Group 3	Group 7
Age	18-55	18-55
Dosage level	60 µg	60 µg
Group	Group 4	Group 5
Age	>55	>55
Dosage level	30 µg	30 µg
Group	Group 5	Group 6
Age	>55	>55
Dosage level	60 µg	60 µg

6.1.2.2. Cohort 2 and Cohort 3 Combined

6.1.2.2.1. Main Analysis

In participants with and without evidence of SARS-CoV-2 infection:

For Superiority Hypothesis Test

- Estimands: GMRs of Omicron(BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 Combined to 1 month after BNT162b2 given as a second booster dose for C4591031 Substudy E Group 1.

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs along with the model-based LS GMT and associated 2-sided 95% CIs will be calculated using the linear regression model that includes terms for baseline neutralizing titer and comparison group. Statistical method is described in Section 5.2.4.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: The LS GMT and associated 95% CIs from each comparison group, as well as the model-based GMR with their associated 95% CIs, will be summarized.

For Noninferiority Hypothesis Test

- Estimands:
    - The difference in percentages of participants with seroresponse to the Omicron strain (BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined to 1 month after BNT162b2 given as a second booster dose for C4591031 Substudy E Group 1
    - GMRs of Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 2 + Cohort 3/Group 1 combined to 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined

  - The difference in percentages of participants with seroresponse to the Omicron strain (BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 2 + Cohort 3/Group 1 combined to 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs along with the model-based LS GMTs and associated 2-sided 95% CIs for each group will be calculated using the linear regression model that includes terms for baseline neutralizing titer and comparison group. Statistical methods described in Section 5.2.4.
  The percentages of participants with seroresponse and the associated Clopper-Pearson 95% CIs for each comparison group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers will be calculated based on the pooled data in 2 comparator groups. Statistical methods are described in Section 5.2.1.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: The LS GMTs and associated 95% CIs from each comparison group, as well as the model-based GMR with their associated 95% CIs, will be summarized. The number/percentages of participants with seroresponse for each comparison group and the corresponding 95% CIs, along the difference in percentages of participants with seroresponse between the 2 comparison groups and the associated 2-sided 95% CIs will be provided.

6.1.2.2.2. Sensitivity Analysis

To support the interpretation of the primary analysis, the unadjusted GMTs and 95% CIs will be provided for each comparison group, both before the study vaccination and 1 month after vaccination. The unadjusted GMR and 95% CIs will also be calculated based on the Student t distribution. Statistical methods are described in Section 5.2.4.

The unadjusted difference in percentages of participants with seroresponse between the 2 comparison groups and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method. Statistical methods are described in Section 5.2.1.

Supportive analyses in participants without evidence of SARS-CoV-2 infection may also be performed.

6.2. Secondary Endpoint(s)

6.2.1. Secondary Immunogenicity Endpoints

6.2.1.1. Main Analysis

For Noninferiority Hypothesis Test

For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):
In participants with and without evidence of SARS-CoV-2 infection:

- Estimands: GMRs of reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined to 1 month after BNT162b2 given as a second booster dose for C4591031 Substudy E Group 1.

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs along with the model-based LS GMTs and associated 2-sided 95% CIs for each group will be calculated using the linear regression model that includes terms for baseline neutralizing titer and comparison group. Statistical method described in Section 5.2.4.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: The LS GMTs and associated 95% CIs from each comparison group, as well as the model-based GMR with the associated 95% CI, will be summarized.

- Supportive Analysis: As supportive analysis, the unadjusted GMTs and 95% CIs at before study vaccination and 1 month after vaccination will be provided for each comparison group. The unadjusted GMR and 95% CIs will also be calculated based on the t-distribution. Statistical methods described in Section 5.2.4. The same analyses in participants without evidence of SARS-CoV-2 infection may also be performed as supportive.

For Descriptive Summary

For Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined:

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- Estimands:
    - GMTs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at each timepoint for each group (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined)
    - GMFRs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to subsequent time points for each group (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined)
    - Percentages of participants with seroresponse to Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at each time point for each group (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined)
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.2.3. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.2.5. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group (Section 5.2.1).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.4/BA.5) and reference-strain–neutralizing titers from baseline to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each group in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection.

6.3. Exploratory Endpoint(s)

6.3.1. COVID-19 Cases

Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.

6.3.2. SARS-CoV-2–Neutralizing Titers Previously Specified for the Respective Cohorts at COVID-19 Illness Visit and Convalescent Visit

SARS-CoV-2–neutralizing titers at the time of a COVID-19 illness visit and at the convalescent visit will be listed for participants with blood sample taken at these visits.

6.3.3. SARS-CoV-2 VOC-Neutralizing Titers For VOCs Not Already Specified

- Estimands:
    - GMTs of SARS-CoV-2 VOC-neutralizing titers for VOCs not already specified at specific timepoint for each group
    - GMFRs of SARS-CoV-2 VOC-neutralizing titers for VOCs not already specified from before the study vaccination to subsequent time points for each group
    - Percentages of participants with seroresponse to SARS-CoV-2 VOC–neutralizing titers for VOCs not already specified at each time point
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.2.3. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.2.5. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group (Section 5.2.1).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2–neutralizing titers for VOCs from baseline (before the study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each group. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group.

6.3.4. Cell-Mediated Immune Response

For Cohort 2, the cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron strain (BA.4/BA.5) will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

6.4. Subset Analyses

For each analysis group, subgroup analyses based on sex and baseline SARS-CoV-2 status will be performed on all primary immunogenicity endpoints as supplemental analyses and for all primary safety endpoints.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination, sex, race, ethnicity, baseline SARS-CoV-2 status, and classification of BMI, will be summarized using descriptive statistics for each group based on the safety population and the evaluable immunogenicity population. Timing and name of all previous doses of COVID-19 vaccinations prior to enrollment will also be summarized for each group.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of participants with at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by group for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized/assigned participants will be included in the disposition summary. In addition, the numbers and percentages of participants who received the study vaccination, who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by group (according to randomized/assigned group assignment). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately along with the reasons for exclusion, by group.

6.5.2.2. Blood Samples for Assay

The number and percentage of randomized/assigned participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for each time point by group.

6.5.2.3. Transmission of E-Diaries

The number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for the study vaccination will be summarized according to the vaccine actually received.

The safety population will be used.

6.5.3. Study Intervention Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized/assigned and receiving the study intervention will be tabulated, for each group and overall, for all randomized/assigned participants in each cohort. The denominator for the percentage calculations is the total number of randomized/assigned participants in the given group or overall.

A listing of participants showing the randomized/assigned vaccine and the vaccine actually received at the study vaccination will be presented.

6.5.3.2. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before the study vaccination will be listed. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated by group. Prohibited medications will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications will be provided. The safety population will be used.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in the Primary Safety Endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below. As Cohort 1, Cohort 2, and Cohort 3 are included in this sponsor open-label Phase 2/3 study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analyses Timing

Statistical analyses will be carried out when the following data are available for each of Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined:

- Safety and immunogenicity data through Visit 3 (1 month after study vaccination)
- Safety and immunogenicity data through Visit 5 (6 months after study vaccination)

Certain analyses may be combined as one regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes.

At the request of regulatory agencies, analyses of 7 days reactogenicity data for Cohort 2 and descriptive summary of immunogenicity data for a subset of Cohort 2/Group 4 participants and C4591031 Substudy E Group 1 will be performed.

8. REFERENCES

1. Collett D. Statistical inference for binary data. Chapter 2. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BLQ	below limit of quantitation
BMI	body mass index
BNT162b2 Bivalent (WT/OMI BA.1)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.1)
BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5
BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529 sublineage BA.2)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
EDMC	external data monitoring committee
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IRT	interactive response technology
IRC	internal review committee
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
OMI	Omicron
PT	preferred term
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
VOC	variant of concern
WHO	World Health Organization
WT	wild type

Document Approval Record

Document Name:	C4591044 Statistical Analysis Plan Clean Copy, V3, 14 Nov 2022
Document Title:	AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2/3 STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BIVALENT BNT162b RNA-BASED VACCINE CANDIDATE AS A BOOSTER DOSE IN COVID-19 VACCINE–EXPERIENCED HEALTHY INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
[redacted]	15-Nov-2022 02:58:05	Final Approval

A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162B2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162B2

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b2 RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT Number:	N/A
Protocol Number:	C4591031
Phase:	3

Brief Title: A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2

Document History

Document	Version Date
Original protocol	13 May 2021

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LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title:

A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. In January 2020, the pathogen causing this outbreak was identified as 2019-nCoV. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 11 February 2020, the virus was officially named as SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19. On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed. To-date, more than 148 million people have been infected with SARS-CoV-2 and >3 million have died, demonstrating an urgent need for efficacious vaccines.

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

Like other COVID-19 vaccines recently developed, the long-term persistence of immunity and efficacy of BNT162b2 has yet to be studied. Furthermore, the efficacy of BNT162b2 in the face of ongoing emergence of new SARS-CoV-2 variants, with multiple mutations in the S protein, is unknown. Therefore, this master protocol will study the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (eg, age groups) having previously received 2 doses of BNT162b2, with the details and rationale for each strategy provided in substudy appendices.

Studying boosting strategies under a single master protocol rather than separate protocols will allow an organized approach that can be easily adapted as data emerge that can impact our understanding of what boosting strategies may be required. This approach will not only be more expeditious to implement, which is critical given the public health emergency the COVID-19 global pandemic represents, but also more readily understandable for investigational sites.

Objectives and Endpoints

Please refer to the substudy appendices for the objectives and endpoints of each substudy.

Estimands

Please refer to the substudy appendices for the rationale of each substudy.

Overall Design

This is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed separately and these substudies may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

Substudy A Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥16 to <55 years of age and approximately 40% of participants ≥55 years of age.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses. The timing of this booster vaccination will also be informed by the outcome of the interim analyses.

Number of Participants

Substudy A will include 10,000 participants.

Data Monitoring Committee or Other Independent Oversight Committee

An external DMC will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods:

The statistical methods will be specified in the respective substudy appendices.

1.2. Schema

Please refer to the appendices for the schema of each substudy.

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.

Refer to the SoA of Substudy A in Section 10.7.1.3.

2. INTRODUCTION

BNT162b2 is an RNA-based COVID-19 vaccine that is currently being investigated for the prevention of COVID-19 in individuals ≥12 years of age. On 02 December 2020, the MHRA in the UK granted a temporary authorization.[1] On 11 December 2020, the US FDA issued an EUA for use in individuals 16 years of age and older. BNT162b2 has now been granted a conditional marketing authorization, EUA, or temporary authorization in a total of more than 60 countries.[2,3,4]

2.1. Study Rationale

Like other COVID-19 vaccines recently developed, the long-term persistence of immunity and efficacy of BNT162b2 has yet to be studied. Furthermore, the efficacy of BNT162b2 in the face of recurring emergence of new SARS-CoV-2 variants, with multiple mutations in the S protein, is unknown. Therefore, this master protocol will evaluate the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (eg, age groups) having previously received 2 doses of BNT162b2 administered 21 days apart, with the details and rationale for each strategy provided in substudy appendices (Section 10.7 onwards).

Studying boosting strategies under a single master protocol, rather than separate protocols, will allow an organized approach that can be easily adapted as data emerge that can impact our understanding of what boosting strategies may be required. This approach will not only be more expeditious to implement, which is critical given the public health emergency the COVID-19 global pandemic represents, but also more readily understandable for investigational sites.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that 2019-nCoV was the underlying cause. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020.[5] On 11 February 2020, the virus was officially named as SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19.[5,6] SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, and on 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[7] To-date, more than 148 million people have been infected with SARS-CoV-2 and >3 million have died, demonstrating an urgent need for efficacious vaccines.[8]

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations.[9]

Recent evolution of SARS-CoV-2 is resulting in an emergence of new virus variants with multiple mutations in the S protein, which might be associated with the lower efficacy of some of the current vaccines. Therefore, there is a need to continue research including new approaches, such as evaluation of booster doses, to overcome waning immunity and/or the development of modified vaccines.[10]

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.[11] The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age, healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. The study consists of 2 parts: Phase 1: to identify the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg [for BNT162b1]); Phase 2/3: an expanded-cohort and efficacy part for the selected vaccine candidate (BNT162b2).

The available immunogenicity data from Phase 1 participants show that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response. BNT162b2 was selected from the Phase 1 part of the study based on the overall safety, tolerability, and immunogenicity. In a mid-November 2020 analysis of 36,621 participants randomized 1:1 to vaccine or placebo, who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination schedule, the efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the active vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.[12]

In a subsequent analysis of 927 confirmed symptomatic cases of COVID-19, an efficacy rate of 91.3% was observed for BNT162b2 in preventing such cases occurring between 7 days to 6 months after the second dose.[13] Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

- 100% in preventing severe disease as defined by the CDC.
- 95.3% in preventing severe disease as defined by the FDA.

- 100% in preventing COVID-19 cases in South Africa, where the B.1.351 lineage is prevalent.

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled through the 14 November 2020 data cutoff (N=43,252, which includes late enrollment of additional adolescent and adult participants) were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.[12]

The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). The frequency of SAEs was low (<0.5%), without meaningful imbalances between study arms. Otherwise, there were no notable patterns or numerical imbalances between vaccine groups for specific categories of nonserious AEs (including other neurologic, neuroinflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, sexes, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.[12]

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no approved or licensed preventive or therapeutic options available. However, based on the data available from the C4591001 study, multiple temporary or EUAs have been granted. The available safety and immunogenicity data from the ongoing Pfizer-BioNTech clinical trial combined with available nonclinical data with BNT162 vaccines and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable benefit/risk profile and support continued clinical development of BNT162b2.

In the C4591001 study, BNT162b2 has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%).[12] Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of participants reporting hypersensitivity-related AEs was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs 111 [0.51%]). Severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in older adults (>55 years of age) (≤2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited AEs, lymphadenopathy occurred much more frequently in the active vaccine group than the placebo group and is plausibly related to vaccination. SAEs, while

uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study.[12]

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. The risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of VAED.[12]

In the latest analysis from C4591001, vaccine safety has been evaluated in more than 44,000 participants ≥16 years of age, with more than 12,000 vaccinated participants having at least 6 months follow-up after their second dose. No serious safety concerns have been observed in this timeframe. Side effects observed in this analysis were generally consistent with previously reported results.[13]

Continued clinical investigation is justified, given:

- the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection.
- the potential of the BioNTech platform of RNA-based vaccines to deliver high numbers of vaccine doses rapidly in a single production campaign.
- the threat posed by the SARS-CoV-2 variants emerging worldwide.
- the potential need for enhancing immunoresponses to overcome waning immunity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 RNA-Based COVID-19 Vaccine		
Local reactions and systemic events may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. The most common events reported in Study C4591001 were mild to moderate pain at the injection site, fatigue, and headache.[12]	• Local reactions and systemic events will be recorded as AEs. • All study participants will be observed for at least 30 minutes after vaccination.
Safety profile of a novel vaccine not yet fully characterized. Adverse reactions (risks) identified from the postauthorization safety data include the following:	Data available from the C4591001 study showed low incidence of severe or serious events and no clinically concerning safety observations across the safety population and within demographic	• Collection of AEs from signing of the ICD through 1 month after the booster vaccination. • Collection of SAEs from signing of the ICD through

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
anaphylaxis, other hypersensitivity reactions (eg, rash, pruritus, urticaria, angioedema), pain in extremity (injected arm), vomiting, and diarrhea.	subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[12] Postauthorization safety data surveillance has confirmed the safety profile observed in C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in this table.	6 months after the booster vaccination. • DMC review throughout the study to review all safety data. • All participants will be observed for at least 30 minutes after vaccination.
Theoretical risk for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with RSV, feline coronavirus, and Dengue virus vaccines. It is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection. No evidence of disease enhancement has been seen in large-scale clinical study of BNT162b2 in humans or in postauthorization surveillance.	Monitoring for cases of COVID-19 developing during the study, which will be reported as AESIs. Assessments of individual cases for disease enhancement is challenging based on current understanding of mechanism of pathogenesis, thus evaluations of any adverse or unexpected imbalances in severe COVID-19 cases may provide insight to a potential signal for this theoretical risk.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	• Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. • Monitoring for cases of COVID-19 developing during the study, which will be reported as AESIs.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in Substudy A are detailed in Section 10.7.2.3.1.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risks to participants participating in each substudy, the potential risks identified in association with BNT162b2 are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

For substudy-specific objectives and endpoints, refer to each respective substudy appendix. For Substudy A, refer to Section 10.7.3.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed in Section 10.7 onwards. Each substudy may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the master protocol study rationale.

See the substudy appendices for the rationales supporting each substudy.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for BNT162b2, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4) if indicated by the substudy eligibility criteria.

4.3. Justification for Dose

Based on data from the Phase 1 component of clinical trial C4591001 and available nonclinical data, the modRNA BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2/3 evaluation of safety, immunogenicity, and efficacy. This is the dose that was shown to be effective and has been authorized for temporary or emergency use.

4.4. End of Study Definition

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

A participant is considered to have completed the (sub)study if he/she has completed all phases of the (sub)study, including the last visit.

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 master protocol criteria apply, as well as substudy specific inclusion criteria:

	Master Protocol Criteria	Substudy A
Type of Participant and Disease Characteristics:		
1. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.	X	
2. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.9.	X	
Informed Consent:		
3. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.	X	
Other Inclusions:		
4. Participants who have received 2 prior doses of 30 µg BNT162b2 19-42 days apart, with the second dose being at least 175 days before Visit 1 (Day 1). Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.	X	
Age and Sex:		
5. Male or female participants ≥16 years of age at Visit 1 (Day 1) who participated in C4591001. • Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.		X

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following master protocol criteria apply, as well as substudy specific exclusion criteria:

	Master Protocol Criteria	Substudy A
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.	X	
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).	X	
3. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.	X	
4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.	X	
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.	X	
6. Women who are pregnant or breastfeeding.	X	
Prior/Concomitant Therapy:		
7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.	X	
8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.	X	
Prior/Concurrent Clinical Study Experience:		
9. Previous participation in other studies involving study intervention containing LNPs.	X	
Other Exclusions:		
10. Investigator site staff or Pfizer-BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.	X	
11. Receipt of medications intended to prevent COVID-19.		X
12. Prior receipt of more than 2 doses of BNT162b2 30 µg.		X
13. Participation in other studies involving study intervention within 28 days prior to study entry, other than C4591001, and/or during study participation.		X

5.3. Lifestyle Considerations

5.3.1. Contraception

The following section is applicable if indicated by the substudy eligibility criteria.

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) considering that their risk for pregnancy may have changed since the last visit. 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 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 SAEs.

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/Administration of Study Intervention

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. Participants meeting these criteria at Vaccination 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

1. Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:

    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;

- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

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

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

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

6. SPECIFIC STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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.

6.1. Study Intervention(s) Administered

For the purposes of the master protocol, study intervention refers to the 30 µg dose level of BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S). Additional study intervention(s) are detailed for each substudy, if applicable. Additional study interventions administered in Substudy A are detailed in Section 10.7.6.

Intervention Name	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	30-µg
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP	IMP
Sourcing	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

6.1.1. Administration

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.

See Section 10.7.6.1.1 for further study intervention administration details for Substudy A.

6.2. Preparation, Handling, Storage, and 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 once diluted.

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 preparation and dispensing.

See Section 10.7.6.1.2 for additional preparation and dispensing details for Substudy A.

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 using 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 Arrangements

Blinding of the arrangement for site personnel and the sponsor for Substudy A are detailed in Section 10.7.6.2.1 and Section 10.7.6.2.2.

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. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention After the End of the Study

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

6.7. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer 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.

6.8. Concomitant Therapy

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

- Any vaccinations received from 28 days prior to study enrollment until 28 days following administration of the last study intervention.
- Prohibited medications listed in Section 6.8.1 will be recorded to include start and stop dates, name of the medication, dose, unit, route, and frequency.

6.8.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward 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 through 28 days after administration of the last study intervention.

- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 within 90 days before enrollment through conclusion of the study.

- Receipt of any other (nonstudy) coronavirus vaccine at any time 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.

6.8.2. Permitted During the Study

Medication other than that described as prohibited in Section 6.8.1 required for treatment of preexisting conditions or acute illness is permitted.

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

Hormonal contraceptives that meet the requirements of this study can be used in participants who are WOCBP (see Appendix 4).

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. Reasons for permanent discontinuation of study intervention 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*).

*A positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. If study intervention (other than Dose 1) has been delayed per Section 5.5, because of febrile or other acute illness (Item 1 in the Section 5.5 list), and the investigator later diagnoses the signs and symptoms as COVID-19 (with or without a positive SARS-CoV-2 NAAT result), the participant may receive a further dose of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and immunogenicity. 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. Participants who remain in the study for evaluation of safety will be contacted by telephone 6 months after their last study vaccination to record AEs as described in Section 8.3.

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 include the following:

- Refused further study procedures;
- 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.

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. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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

See Section 10.7.8 for assessments and procedures specific to Substudy A.

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

The 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.

8.1. Efficacy Assessments and/or Immunogenicity Assessments

Serum samples may be obtained for immunogenicity testing at the visits specified in the substudy SoA and assays performed as detailed for each substudy.

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 genetic material 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 genetic material 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 their 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 30 minutes after administration of the study intervention will be assessed and documented in the AE CRF.

8.2.1. Physical Examinations

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

The participant's body temperature will be measured prior to each vaccination.

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.2.4. 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. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

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).

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

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

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

For all participants, information about AEs will be collected for events occurring within approximately 1 month after each vaccination, and information about SAEs will be collected for events occurring approximately 6 months after each vaccination.

Substudy A

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian

provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2, and from Visit 101 to Visit 102.

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to Visit 3 (approximately 6 months after the booster vaccination), and from Visit 101 to 103 (approximately 6 months after participants who originally received placebo are administered BNT162b2).

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.

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 permanently 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 information on 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, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

After the initial AE or 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 toward 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. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An

environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study 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 EDP:
    - 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 28 days 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

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the Vaccines SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

8.3.7.1. Substudies Including a Potential COVID-19 Illness Visit

The following substudies include a potential COVID-19 illness visit: Substudy A.

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

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

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

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

OR

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

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

8.3.7.2. Substudies NOT Including a Potential COVID-19 Illness Visit

For substudies not including a potential COVID-19 illness visit, confirmed COVID-19 diagnoses will be considered AESIs (Section 8.3.8).

All substudies in the current version of the master protocol include a potential COVID-19 illness visit.

8.3.8. Adverse Events of Special Interest

This section is not applicable for substudies including a potential COVID-19 illness visit.

All substudies in the current version of the master protocol include a potential COVID-19 illness visit.

8.3.8.1. Substudies NOT Including a Potential COVID-19 Illness Visit

This section provides information on AESIs that may be detected during the study:

- Confirmed COVID-19 diagnosis (clinical signs/symptoms and positive SARS-CoV-2 NAAT test)

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccines SAE Report Form.

8.3.8.2. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

Safety Event	**Recorded on the CRF**	**Reported on the 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 within 24 hours.

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

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

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

8.5.1. Specified Genetics

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

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Statistical Hypotheses

9.1.1. Estimands

For estimands refer to the respective appendix for each substudy. For Substudy A, refer to Section 10.7.3.

9.1.2. Statistical Hypotheses

For Substudy A, refer to Section 10.7.9.1.2 for hypotheses.

9.1.3. Multiplicity Adjustment

For Substudy A, refer to Section 10.7.9.1.3 for multiplicity adjustment.

9.2. Analysis Sets

For analysis sets, refer to respective appendix for each substudy. For Substudy A, refer to Section 10.7.9.2.

9.3. Statistical Analyses

The SAP will be developed and finalized for each substudy before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the general considerations of statistical analyses.

Refer to each substudy appendix for description of the statistical analyses for primary, secondary, and/or exploratory endpoints. For Substudy A, refer to Section 10.7.9.3.

9.3.1. General Considerations

Each substudy will be reported separately.

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the vaccine group to which they were randomized. Missing laboratory results will not be imputed.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method). The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.

The 3-tier approach may be used to summarize AEs for certain substudies (refer to each substudy for specification). For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic

p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

9.3.1.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

9.3.1.2.1. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

9.3.1.2.2. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

9.4. Interim Analyses

Interim analyses will be determined by substudy, and details are provided in each corresponding appendix as necessary.

9.5. Sample Size Determination

Sample size will be determined by substudy, and details are provided in each corresponding appendix.

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her parent(s)/legal guardian(s) and answer all questions regarding the study. The participant or his/her parent(s)/legal guardian(s) 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 or their parent(s)/legal guardian(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his/her parent(s)/legal guardian(s) 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 or his/her parent(s)/legal guardian(s) 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 or his/her parent(s)/legal guardian(s).

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

The investigator further must ensure that each study participant or his/her parent(s)/legal guardian(s) 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 on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

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

A copy of the ICD(s) must be provided to the participant or his/her parent(s)/legal guardian(s).

Participants who are rescreened are required to sign a new ICD.

10.1.4. 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 ID. 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators, as appropriate.

Any further involvement of the DMC in each substudy is specified in the corresponding substudy appendix.

See Section 10.7.9.4.2 for details of the DMC's role in Substudy A.

10.1.6. 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 data from these trials available 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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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 retain 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.

10.1.8. 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 and its origin can be found in the study monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the study monitoring plan, which is maintained by the sponsor.

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. 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/CRO 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 the ICH 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.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. 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/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

If required based on each substudy design and participant population, a pregnancy test will be performed at times defined in the SoA section of each substudy.

- Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for participants who are WOCBP.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New condition 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 or 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 that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccines SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2)

nonserious 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	All AEs or SAEs associated with exposure during pregnancy or breastfeeding Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccines SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccines SAE Report Form.

** **EDB** is reported to Pfizer Safety using the Vaccines SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccines SAE Report Form.

- When an AE or 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 or 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 or 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 or 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 or SAE. The investigator will use clinical judgment to determine the relationship.

- 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.
- 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 or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 submitted documents.
- 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 an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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 and Barrier Guidance

The following appendix applies as specified in each substudy eligibility criteria section.

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 contraception/barrier as detailed below:
  - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

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

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

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

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - A 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 (eg, bilateral tubal ligation).

5. Vasectomized partner:

   - A 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 “adaptors” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure 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 Hy's law cases, 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, or 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, 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: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

10.6.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.7. Appendix 7: Substudy A:

10.7.1. Substudy Summary

10.7.1.1. Synopsis

See Section 1.1 for a synopsis of Substudy A.

10.7.1.2. Schema

	Visit Number	1	2	3	4	Unplanned
	Visit Description	**Booster Vaccination**	**1-Month Telephone Contact**	**6-Month Follow-up Visit**	**12-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Participants having received 2 prior doses of 30 µg BNT162b2 at least 6 months prior to randomization	Group 1 (n=5000)	BNT162b2				
	Group 2 (n=5000)	Placebo				
	Blood draw	20 mL		20 mL		

Visit Number	101	102	103	Unplanned
Visit Description	**BNT162b2 Vaccination**	**1-Month Telephone Contact 2**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Group 2	BNT162b2			
Blood Draw	20 mL			

10.7.1.3. Schedule of Activities

Visit Number	1	2	3	4	Unplanned
Visit Description	**Booster Vaccination**	**1-Month Telephone Contact**	**6-Month Follow-up Visit[a]**	**12-Month Telephone Contact[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window	**Day 1[c]**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**350 to 378 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X				
Obtain the participant's prior participant number from Study C4591001	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment[d]	X				
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	X	
Measure height and weight	X				
Measure temperature (body)	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X	X			
Collect nonstudy vaccine information	X	X			
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity assessment	~20 mL		~20 mL		
Obtain nasal (midturbinate) swab	X				X
Obtain randomization number and study intervention allocation	X				
Administer study intervention	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Explain participant communication methods, assist the participant with downloading the app, or issue provisioned device, if required	X				

Visit Number	1	2	3	4	Unplanned
Visit Description	**Booster Vaccination**	**1-Month Telephone Contact**	**6-Month Follow-up Visit[a]**	**12-Month Telephone Contact[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window	**Day 1[c]**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**350 to 378 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Provide/ensure the participant has a thermometer	X				
Request the participant return the e-diary or assist the participant to delete the application				X	
Collect AEs and SAEs as appropriate	X	X	X[e]		X[f]
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)					X
Contact the participant by telephone		X		X	

a. This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined BNT162b2 booster vaccination.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
d. Including, if indicated, a physical examination.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
f. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

10.7.1.3.1. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo will have the opportunity to receive BNT162b2 as part of the study if indicated by, and at a time informed by, the outcome of the interim analyses detailed in Section 10.7.9.4.

Visit Number	101	102	103	Unplanned
Visit Description	**BNT162b2 Vaccination**	**1-Month Telephone Contact 2**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window	**As Informed by the Outcome of the Interim Analyses**	**28 to 35 Days After Visit 101**	**175 to 189 Days After Visit 101**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant originally received placebo	X			
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	
Perform urine pregnancy test (if appropriate)	X			
Confirm use of contraceptives (if appropriate)	X			
Collect prohibited medication use	X	X	X	X
Confirm eligibility	X			
Review temporary delay criteria	X			
Collect blood sample for immunogenicity assessment	~20 mL			
Obtain nasal (midturbinate) swab	X			X
Obtain vaccine vial allocation via IRT	X			
Administer BNT162b2	X			
Assess acute reactions for at least 30 minutes after study intervention administration	X			
Request the participant return the e-diary or assist the participant to delete the application			X	
Collect AEs and SAEs as appropriate	X	X	X	X[a]
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)				X
Contact the participant by telephone		X	X	

Abbreviations: COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; IRT = interactive response technology.
a. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

10.7.2. Introduction

10.7.2.1. Study Rationale

Substudy A will evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2 when administered to participants having previously received 2 doses of BNT162b2 at least 6 months prior to randomization.

10.7.2.2. Background

See Section 2.2 for the study background.

10.7.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy A beyond those detailed for the master study (see Section 2.3).

10.7.2.3.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy A may be:

- Receipt of a booster dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Access to COVID-19 diagnostic testing.
- Contributing to research to help others in a time of global pandemic.

10.7.3. Objectives, Endpoints and Estimands

Objectives	Estimands	Endpoints
Primary Efficacy	**Primary Efficacy**	**Primary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose	• AEs • SAEs
Secondary Efficacy	**Secondary Efficacy**	**Secondary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against asymptomatic infection in participants without evidence of past SARS-CoV-2 infection	In complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion
Exploratory		
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received the BNT162b2 booster dose	In participants who received BNT162b2 at the booster vaccination (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	Confirmed COVID-19 incidence per 1000 person-years of follow-up

10.7.4. Study Design

10.7.4.1. Overall Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo as shown in Section 10.7.1.2. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥16 to <55 years of age and approximately 40% of participants ≥55 years of age. Approximately 10,000 participants will be randomized in the study. Assuming a 15% nonevaluable rate, there will be approximately 4250 evaluable participants in each group.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses, as outlined below in Section 10.7.4.2.1 and further detailed in Section 10.7.9.4. The timing of this booster vaccination will also be informed by the outcome of the interim analyses detailed in Section 10.7.9.4.

10.7.4.2. Scientific Rationale for Substudy A Design

See Section 10.7.2.1.

10.7.4.2.1. Statistical Rationale for Substudy A Design

In addition to assessing the safety of administering a booster dose in a large number of participants, a key objective of this study is to characterize the potential for waning VE over time in participants who do not receive a booster. It is important to identify when a booster is needed to protect the participants in this trial, as well as to inform vaccine policy decision-makers. Consequently, the most appropriate statistical framework to facilitate decision-making in this setting is periodic statistical summaries (every 2 months over the scheduled 6-month follow-up period) using statistical guidelines, rather than the traditional hypothesis testing framework with strong control of overall type 1 error across analysis time points.

Using a traditional hypothesis testing framework, a policy of recommending a booster would be implemented only if the lower limit of the alpha-adjusted CI for VE of the boosted group relative to the unboosted group was greater than some specified value (eg, 20% or 30%). This approach controls the overall type 1 error, that is, deciding that a booster is necessary to maintain VE when it is actually not necessary. But strong control of type 1 error inflates type 2 error for a fixed sample size. And in this setting, type 2 error, that is, deciding that a booster is not necessary when it actually is, has a greater negative impact on public health.

For this reason, a descriptive statistical approach will be used with point estimates of VE (boosted relative to unboosted) and unadjusted (for multiplicity) 95% CIs at each time point (2, 4, and 6 months). In addition, to help put these results into perspective, an inferred VE for the unboosted group (relative to an unvaccinated population) will be calculated. Specifically, assuming that the newly boosted group has the same VE (relative to an unvaccinated population) over time that was observed in the parent C4591001 trial, an

inferred unvaccinated (placebo) disease rate can be obtained at various time points and used to calculate the inferred VE (relative to unvaccinated) for the unboosted group. If this value is lower than a specified value (eg, 60%) at a given analysis time point, then a decision to offer a booster to the unboosted participants at that time may be implemented.

10.7.4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics shown to reflect that achieved in C4591001.[14]

10.7.4.3. Justification for Dose

See Section 4.3 for a justification of the BNT162b2 dose used in Substudy A.

10.7.4.4. End of Study Definition

See Section 4.4.

10.7.5. Study Population

Details of the master and Substudy A eligibility criteria are shown in Section 5. Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy A–specific inclusion and exclusion criteria.

10.7.5.1. Lifestyle Considerations

Contraception requirements will apply to Substudy A as detailed in Section 5.3 and Section 10.4.

10.7.5.2. Screen Failures

See Section 5.4.

10.7.5.3. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.7.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

10.7.6.1. Study Intervention(s) Administered

See Section 6.1 for details of BNT162b2.

Additional Intervention Name	Saline Placebo
Type	Placebo
Dose Formulation	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	N/A
Dosage Level(s)	N/A
Route of Administration	Intramuscular injection
Use	Placebo
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	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

10.7.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 1 in accordance with the substudy's SoA (Section 10.7.1.3).

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

Study intervention at Visit 101 will be conducted in an open-label manner.

10.7.6.1.2. Preparation and Dispensing

For booster vaccination during Substudy A, study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure the participants remain blinded.

10.7.6.2. Measures to Minimize Bias: Randomization and Blinding

10.7.6.2.1. Blinding of Site Personnel

In this observer-blinded substudy, 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 there are differences in physical appearance of the study interventions, the study intervention will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must

not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The study will be unblinded to site personnel at a time informed by the outcome of the interim analyses as detailed in Section 10.7.9.4.

10.7.6.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 10.7.9.4.2). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

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

The study will be unblinded to all sponsor/Pfizer staff at a time informed by the outcome of the interim analyses as detailed in Section 10.7.9.4.

10.7.6.2.3. 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.

10.7.6.3. Study Intervention Compliance

See Section 6.4.

10.7.6.4. Dose Modification

See Section 6.5.

10.7.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.7.6.6. Treatment of Overdose

See Section 6.7.

10.7.6.7. Concomitant Therapy

See Section 6.8.

10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.7.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is approximately up to 60 mL.

For all participants, 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.

10.7.8.1. Efficacy and/or Immunogenicity Assessments for Substudy A

10.7.8.1.1. Efficacy Against COVID-19

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 10.7.8.5.5.1), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[15] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA-approved under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (ie, NAAT) to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 10.7.8.5.5.1) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

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

- Diarrhea;
- Vomiting.

- Confirmed severe COVID-19 (FDA definition[16]): confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an ICU;
  - Death.
- Confirmed severe COVID-19 (CDC definition[17]): confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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

10.7.8.1.2. Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection will be evaluated through impact on the seroconversion of N-binding antibody.

Blood samples for assessment of N-binding antibodies are drawn at Visits 1 and 3. An asymptomatic case of SARS-CoV-2 infection based on the seroconversion of N-binding antibody is defined as positive N-binding antibody at Visit 3 in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and at the time of a potential COVID-19 illness).

10.7.8.2. Safety Assessments

See Section 8.2.

10.7.8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.7.8.4. Immunogenicity Assessments

See Section 8.1.

10.7.8.5. Substudy A Procedures

10.7.8.5.1. Visit 1 – Booster Vaccination (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior participant number from Study C4591001 and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.4.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 10.7.8.5.6), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
    - Provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.7.8.5.6 for further details.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

10.7.8.5.2. Visit 2 – 1-Month Telephone Contact (28 to 35 Days After Visit 1)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in Section 5.3.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- 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.

10.7.8.5.3. Visit 3 – 6-Month Follow-up Visit (175 to 189 Days After Visit 1)

This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined the BNT162b2 booster vaccination.

- Record SAEs as described in Section 8.3.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 2 (if any).
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- 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.

10.7.8.5.4. Visit 4 – 12-Month Telephone Contact (350 to 378 Days After Visit 1)

This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined the BNT162b2 booster vaccination.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect the participant's e-diary or assist the participant in removing 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.

10.7.8.5.5. COVID-19 Surveillance (All Substudy A Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 10.7.8.5.6) 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.

10.7.8.5.5.1. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including
        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
        - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
        - Significant acute renal, hepatic, or neurologic dysfunction
        - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
    - Clinical diagnosis

- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, LFTs, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.6. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.

- If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

10.7.8.5.7. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 1 and Visit 101: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection.

- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 101 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.7.8.5.8. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo will have the opportunity to receive BNT162b2 as part of the study if indicated by, and at a time informed by, the outcome of the interim analyses detailed in Section 10.7.9.4.

10.7.8.5.8.1. Visit 101 – BNT162b2 Vaccination

- Unblind the participant's study intervention assignment (if information not already available), and confirm the participant originally received only placebo at the booster vaccination visit. Secondary confirmation by another site staff member is required.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.4.

- Discuss contraceptive use as described in Section 5.3.1.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).

- Review and consider inclusion criteria and exclusion criteria prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

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

- Record AEs as described in Section 8.3.

- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3), a second sample need not be collected.

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

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.

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

- Complete the source documents.

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

10.7.8.5.8.2. Visit 102 – 1-Month Telephone Contact 2 (28 to 35 Days After Visit 101)

- Contact the participant/participant's parent(s)/legal guardian by telephone.

- Record AEs as described in Section 8.3.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.8.3. Visit 103 – 6-Month Telephone Contact (175 to 189 Days After Visit 101)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 102 (if any).
- Collect the participant's e-diary or assist the participant in removing the study application from his or her own personal device.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.9. Statistical Considerations for Substudy A

See Section 9 for master protocol statistical considerations and substudy specifics below.

10.7.9.1. Statistical Hypotheses

10.7.9.1.1. Estimands

The estimands corresponding to the primary, secondary, and exploratory objectives are described in the table in Section 10.7.3.

In the primary safety objective evaluations, missing AE start 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 efficacy objectives are based on the evaluable efficacy population (Section 10.7.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed for the all-available efficacy populations. Missing laboratory results will not be imputed.

10.7.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.7.9.1.3. Multiplicity Adjustment

No multiplicity adjustment is needed for the study as there is no statistical hypothesis.

10.7.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable efficacy	All eligible randomized participants who receive the booster vaccination as randomized and have no other important protocol deviations as determined by the clinician.
All-available efficacy (mITT)	All randomized participants who receive at least 1 dose of the study intervention.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

10.7.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This

section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.7.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

10.7.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose. The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time. In addition, a summary of VE over different time intervals (ie, prior to 2 months, from 2 months to 4 months, and from 4 months to 6 months after the booster dose, etc), along with the associated 2-sided 95% CI, will be calculated using the same method. **Ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** The point estimate of VE and the associated 2-sided 95% CI, including VE at different time intervals, will be calculated using the same method as for the first primary endpoint described above.
Safety	AEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from the booster dose to 1 month after the booster dose will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is 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. Analyses methods are described in Section 9.3.1.1.

Endpoint	Statistical Analysis Methods
	SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the booster dose to 6 months after the booster dose will be provided for each vaccine group.

10.7.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Efficacy	**Ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection for the active vaccine group to the placebo group** For each of the above efficacy endpoints, the point estimate of VE and the associated 2-sided 95% CI for VE will be calculated using the same method as for the first primary endpoint described above.

10.7.9.3.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
Efficacy	**Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at the booster vaccination** Incidence rates (per 1000 person-years of follow-up) and 2-sided 95% CIs based on Poisson distribution for confirmed COVID-19 illness from 7 days after the second dose will be provided for participants who received BNT162b2 at initial randomization and subsequently, respectively.

10.7.9.4. Interim Analyses

In this substudy, interim efficacy analyses will be performed every 2 months by an unblinded statistical team to inform the timing of administration of BNT162b2 to those originally assigned to placebo. The first interim analysis will be performed after all participants reach 2 months of blinded follow-up. The final efficacy analyses to assess the primary and secondary efficacy objectives are planned to be conducted when all participants complete blinded follow-up (planned to be approximately 175 days after the vaccination at Visit 1 but could be earlier or later depending on the outcome of the interim analyses).

At each interim analysis, the following 2 estimates of VE will be obtained: (1) VE of the BNT162b2 booster group to the nonbooster group (placebo), which is the primary estimand defined for this substudy and directly estimable using the data observed in this substudy, and (2) VE of the nonbooster group (who received a primary series of 2 doses of BNT162b2 approximately 6 months prior to enrollment in this study and did not receive the BNT162b2 booster) relative to an unvaccinated population (never received a BNT162b2 primary series, not observable in this study). These estimates will be obtained using the following derivations.

Let .. $_{12}$ be the VE of the BNT162b2 booster group relative to the nonbooster group, VE_1 be the VE of the BNT162b2 booster group relative to an unvaccinated population, VE_2 be the VE of the nonbooster group relative to an unvaccinated population, IR_1 be the incidence rate of COVID-19 illness in the BNT162b2 booster group, IR_2 be the incidence rate of COVID-19 illness in the placebo booster group, and IR_0 be the nonobservable incidence rate in the unvaccinated population;

(1) VE_{12} can be estimated by observed IR_1 and IR_2 in the study as $VE_{12} = 1 - \frac{IR_1}{IR_2}$;

Since $VE_1 = 1 - \frac{IR_1}{IR_0}$, $VE_2 = 1 - \frac{IR_2}{IR_0}$,

(2) VE_2 can then be estimated by observed IR_1 and IR_2 in the study and an assumed VE_1 as

$VE_2 = 1 - \frac{IR_2(1-VE_1)}{IR_1}$.

Although VE_1 is also not observable from the study, it is expected that VE after the booster dose will be similar to that after the first 2 vaccine doses. Based on the results of the updated efficacy analyses from Study C4591001, the VE from 7 days to 2 months, from 2 to 4 months, and from 4 to 6 months after Dose 2 were approximately 96%, 90%, and 84%, respectively. After 6 months, a 6% drop in VE every 2 months will be assumed. These assumed values of VE_1 will be used to estimate VE_2 at the interim analyses.

If the point estimate of VE_2 (nonbooster group relative to unvaccinated population) in a 2-month interval (ie, 7 days to 2 months, 2 to 4 months, etc.) at the interim analysis is <60%, the study will be unblinded and the placebo group participants may receive BNT162b2 earlier than approximately 175 days after the vaccination at Visit 1. If VE_2 remains ≥60% at the interim analyses, all participants may remain blinded in the study and placebo recipients may not be offered BNT162b2 booster until the 12-month visit. In addition, the placebo group participants may not receive BNT162b2 as part of the study if VE_2 is ≥60% at the final analysis.

10.7.9.4.1. Analysis Timing

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

- Interim efficacy analyses after all participants reach 2 months of blinded follow-up and every 2 months afterwards;
- Efficacy and safety analysis when all participants completed blinded follow-up;
- Efficacy and safety analysis at the end of the study.

10.7.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

This substudy will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

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

- Contemporaneous review of related AEs up to 1 month after the booster vaccination
- Contemporaneous review of all SAEs up to 6 months after the booster vaccination
- At the time of the planned interim analyses, and ad hoc if requested by the unblinded team, review of COVID-19 cases for an adverse imbalance of COVID-19 cases and/or severe COVID-19 cases between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions,

which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10.7.9.5. Sample Size Determination

The sample size of the study is determined to accrue sufficient COVID-19 cases for the VE assessment. Assuming a 15% nonevaluable rate, with 10,000 participants randomized in a 1:1 ratio to receive BNT162b2 booster or placebo, there will be approximately 4250 evaluable participants in each group. Table 1 presents assumptions of VE at various time intervals after the booster dose and the expected number of COVID-19 cases within each time interval with 4250 evaluable participants in each group. If the underlying incidence rate in the unvaccinated population is 0.14 per person-year follow-up, the study will accrue approximately 127 cases in 6 months. If, due to vaccination rollout and other public health measures, the incidence rate drops by 50%, approximately 63 cases are expected to be accrued in 6 months.

Table 1. Expected Number of COVID-19 Cases Under Assumed Vaccine Efficacy and Incidence Rate

Follow-up Time Postbooster	Assumed VE			Expected Number of Cases With 4250 Evaluable Participants Per Group			
	VE_1	VE_2	VE_{12}	IR_0 = 0.14/pyr		IR_0 = 0.07/pyr	
				Boosted	Nonboosted	Boosted	Nonboosted
7 Days to 2 months	96%	72%	85.7%	3	24	2	12
2 to 4 Months	90%	66%	70.6%	10	34	5	17
4 to 6 Months	84%	60%	60.0%	16	40	8	20
7 Days to 4 months	92.8%	68.8%	76.9%	13	58	7	29
7 Days to 6 months	89.8%	65.8%	70.2%	29	97	15	49

Abbreviations: IR_0 = assumed underlying incidence rate in unvaccinated population. The observed incidence rate in placebo group of study C4591001 was 0.14 per person-year follow-up; pyr = person-years; VE_1 = vaccine efficacy of BNT162b2 booster group relative to unvaccinated population, assumed to be similar to the vaccine efficacy after the primary vaccination series observed in study C4591001; VE_2 = vaccine efficacy of nonbooster group relative to unvaccinated population, assumed to have 6% drop every 2 months after the primary vaccination series and the average time after primary vaccination series at study entry is approximately 8 months for participants enrolled in this substudy; VE_{12} = vaccine efficacy of BNT162b2 booster group to nonbooster group, calculated by $VE_{12}=1-(1-VE_1)/(1-VE_2)$.

Table 2 shows the probability to show the lower limit of the 95% CI for VE >30% for a given number of cases observed in the study under various assumed values of VE. For example, if the VE of the booster group relative to the nonbooster group is 70% over 6 months of blinded follow-up, 70 cases will provide 88.9% probability to show that the lower limit of the 95% CI for VE is >30%.

Table 2. Probability for Vaccine Efficacy Assessment

Assumed True VE	Probability to Show Lower Limit of 95% CI for VE >30% With Given Total Number of Cases				
	30 cases	50 cases	70 cases	90 cases	110 cases
60%	0.204	0.411	0.560	0.666	0.744
65%	0.306	0.579	0.743	0.842	0.902
70%	0.443	0.750	0.889	0.950	0.978
75%	0.607	0.889	0.970	0.992	0.998
80%	0.777	0.969	0.996	>0.999	>0.999

For safety outcomes, Table 3 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 0.1%, with 5000 participants in a vaccine group, there is 99% probability of observing at least 1 AE.

Table 3. Probability of Observing at Least 1 AE by Assumed True Event Rates

Sample Size (N)	Assumed True Event Rate of an AE							
	0.01%	0.05%	0.1%	0.2%	0.5%	1%	2%	5%
5000	0.39	0.92	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computerized tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
e-diary	electronic diary
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise

Abbreviation	Term
GMR	geometric mean ratio
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G
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
IRT	interactive response technology
IWR	interactive Web-based response
LFT	liver function test
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
QTL	quality tolerance limit

Abbreviation	Term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAED	vaccine-associated enhanced disease
VE	vaccine efficacy
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

10.9. Appendix 9: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria:

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg-negative, anti-HBe–positive;
- Serum HBV DNA <2000 IU/mL;
- Persistently normal ALT and/or AST levels;
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

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A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b2 RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT Number:	2021-005197-25
Protocol Number:	C4591031
Phase:	3

Brief Title: A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2

Document History

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Amendment 10	22 Jul 2022
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Amendment 2	27 Aug 2021
Amendment 1	27 May 2021
Original protocol	13 May 2021

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

Amendment 10 (22 July 2022)

Overall Rationale for the Amendment:

Initial immunogenicity data reviewed from Cohort 3 Substudy D at 1 month after Dose 2 demonstrated a more pronounced antibody response against the Omicron variant versus the Wild Type and Delta variants. Therefore, the third dose for participants in Cohort 3 of Substudy D has been changed from BNT162b2 OMI 30 µg to BNT162b2 30 µg to provide participants with wider protection against the different SARS-CoV-2 variants, in addition to the protection they will already have against the Omicron variant from their first 2 vaccinations.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 – Synopisis and Section 10.10.4.1 – Overall Design (Substudy D)	Confirmed that if participants do not consent to receive BNT162b2 as a third dose, they will not receive a third dose	Protocol clarification	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.10.6.1.1 – Administration (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 10.10.8 – Study Assessments and Procedures (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 10.10.1.3.3 – Cohort 3 schedule of activities (Substudy D)	Confirmed that the vaccine received at Visit 506 is BNT162b2	Protocol clarification	Substantial
Section 10.10.2.1 – Study Rationale (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 10.8.8.3.5 – Visit 205 – 1 Month Follow-Up Visit (After Vaccination 2) (28-35 Days After Visit 203) (Substudy B)	Confirmed that a participant may be unblinded at Visit 205, 1 month after receiving their second study vaccination, to confirm the date of BNT162b2 receipt	Protocol clarification	Substantial
Section 10.10.1.2.3 – Participants in Cohort 3 schema (Substudy D)	Confirmed that the vaccine received at the 6-month visit is BNT162b2	Protocol clarification	Substantial
Section 1.1 – Synopsis, Section 10.10.1.2 – Schema, Section 10.10.1.3 – Schedule of Activities for Substudy D, Section 10.10.2.1 – Study Rationale, Section 10.10.4 – Study Design, Section 10.10.6.1.1 – Administration, and Section 10.10.8 – Study Assessments and Procedures (Substudy D)	Clarified that participants in Cohort 3 will receive BNT162b2 rather than BNT162b2 OMI as their third dose	Protocol clarification	Substantial
Section 1.1 – Synopsis, Section 10.8.1.2 – Schema, Section 10.8.1.3 – Schedule of Activities for Substudy B, Section 10.8.2.1 – Study Rationale, Section 10.8.4 – Study Design, Section 10.8.5.1 – Inclusion Criteria, and Section 10.8.8.3 – Substudy B Procedures (Substudy B)	Added the number of days since the last dose, in parentheses after the number of months	Protocol clarification	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 – Synopsis, Section 10.9.1.2 – Schema, Section 10.9.1.3 – Schedule of Activities for Substudy C, Section 10.9.2.1 – Study Rationale, Section 10.9.4 – Study Design, and Section 10.9.8.4 – Substudy C Procedures (Substudy C)	Added the number of days since the last dose, in parentheses after the number of months	Protocol clarification	Nonsubstantial
Section 1.1 – Synopsis, Section 10.11.4 – Study Design, and Section 10.11.5.1 – Inclusion Criteria (Substudy E)	Added the number of days since the last dose, in parentheses after the number of months	Protocol clarification	Nonsubstantial
Section 10.7.3 – Objectives, Estimands, and Endpoints (Substudy A)	Deleted the objective for efficacy against asymptomatic SARS-CoV-2 infection	Protocol clarification	Nonsubstantial
Section 10.7.8.1.2 – Efficacy Against Asymptomatic SARS-CoV-2 Infection (Substudy A)	Deleted the section on efficacy against asymptomatic SARS-CoV-2 infection	Protocol clarification	Nonsubstantial
Section 10.7.9.3.3 – Secondary Endpoints(s)/Estimand(s) Analysis (Substudy A)	Deleted the objective for efficacy against asymptomatic SARS-CoV-2 infection	Protocol clarification	Nonsubstantial
Section 10.8.5.2 – Exclusion Criteria, Other Exclusions (Substudy B)	Clarified that prior receipt of more than 3 doses of BNT162b2 30 µg is an exclusion	Protocol clarification	Nonsubstantial
Section 10.8.8.3.3 – Visit 203 –Vaccination 2 (28 to 35 Days After Visit 201) (Substudy B)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.1.3.3 – Cohort 3 schedule of activities (Substudy D)	Extended the visit window by 7 days to 199 days after Visit 502	Protocol clarification	Nonsubstantial
Section 10.10.3 – Objectives, Estimands, and Endpoints (Substudy D)	Added Group 5 to the objectives and clarified the estimands to included those with or without serological or virological evidence of past SARS-CoV-2 infection	Clarified objectives and estimands	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.10.8.6.1.2 – Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401) (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.8.6.2.3 – Visit 404 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 401, or 85 to 123 Days After Visit 401 for Those Participants Who Consent to Receive Substudy D Vaccination 2) (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.8.6.3.2 – Visit 502 – Vaccination 2 (19 to 23 Days After Visit 501) (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.8.6.3.6 – Visit 506 – 6-Month Follow-Up Visit (After Vaccination 2) (150 to 199 Days After Visit 502) and Administration of Vaccination 3 (Substudy D)	Confirmed that a positive SARS-CoV-2 NAAT result without symptoms, or a COVID-19 diagnosis, should not result in discontinuation of study intervention	Protocol clarification	Nonsubstantial
Section 10.10.9.3.2 – Primary Endpoint(s)/Estimand(s) Analysis (Substudy D)	Updated an immunogenicity endpoint to specify the Cohort 1 and 2 participants to be used in analysis	Clarified primary endpoints	Nonsubstantial
Section 10.11.3 – Objectives, Estimands, and Endpoints (Substudy E)	Clarified an exploratory objective's footnote to specify that the subset taken will be from the youngest 150 participants in Substudy E who received bivalent BNT162b2	Clarified the subset of participants to be selected for the exploratory objective	Nonsubstantial
Section 10.11.9.1.2 – Statistical Hypotheses (Substudy E)	Clarified that the primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated by the statistical hypotheses described in the section, and the immunogenicity objectives for participants 18 through 55 years of age are descriptive only	Clarified the statistical hypotheses	Nonsubstantial
Section 10.11.9.1.3 – Multiplicity Adjustment (Substudy E)	Clarified the age ranges for the objectives	To clarify the age ranges to use multiplicity adjustments	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.11.9.3 – Statistical Analyses (Substudy E)	Confirmed that a sensitivity analysis of GMR and difference in seroresponse rate for between-group comparison may be performed	Clarified additional analyses being performed	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title:

A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. In January 2020, the pathogen causing this outbreak was identified as 2019-nCoV. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 11 February 2020, the virus was officially named as SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19. On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed. To-date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died, demonstrating an urgent need for efficacious vaccines.

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

Genetic lineages of SARS-CoV-2 have been emerging and circulating around the world since the beginning of the COVID-19 pandemic. There have been at least 12 different variants identified since December 2020. Within the first 3 months of the start of this global pandemic, the Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), and Epsilon (B.1.427 and B.1.429) variants were identified as VOCs. This is defined as a variant for which there is evidence of an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatment or vaccines, or diagnostic detection failures. On 21 September 2021, these variants were downgraded to variants being monitored. However, current VOCs include Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages). Delta, which has increased transmissibility, has dominated the number of infections in the latter half of 2021. Since the Omicron variant has been newly identified at the time of this protocol amendment, additional information will be learned as time progresses.

A 2-dose series of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older after a median follow-up period of 2 months after the second dose. However, as presented in April 2021, the efficacy of BNT162b2 from 7 days through up to 6 months after the second dose had decreased to 91.3% effective against COVID-19.

However, the vaccine was 100% effective against severe disease as defined by the US CDC, and 95.3% effective against severe COVID-19 as defined by the FDA. Recent data from interim analysis of C4591031 Substudy A have demonstrated that a booster dose administered to individuals who previously received a primary 2-dose series of BNT162b2 restored vaccine protection against COVID-19 to the high levels achieved after the second dose, showing a relative VE of 95.6% when compared to those who did not receive the booster. However, the efficacy of BNT162b2 in the face of ongoing emergence of new SARS-CoV-2 variants, with multiple mutations in the S protein, is unknown. Therefore, the substudies within this master protocol will study the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (eg, age groups), with the details and rationale for each strategy provided in substudy appendices.

Studying boosting strategies under a single master protocol rather than separate protocols will allow an organized approach that can be easily adapted as data emerge that can impact our understanding of what boosting strategies may be required. This approach will not only be more expeditious to implement, which is critical given the public health emergency the COVID-19 global pandemic represents, but also more readily understandable for investigational sites.

Objectives and Endpoints

Please refer to the substudy appendices for the objectives and endpoints of each substudy.

Estimands

Please refer to the substudy appendices for the rationale of each substudy.

Overall Design

This is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed separately and these substudies may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

Substudy A Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥16 to 55 years of age and approximately 40% of participants >55 years of age.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses, or at the discretion of the study sponsor. The timing of this booster vaccination may be informed by the outcome of the interim analyses or at a time decided by the sponsor.

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

Substudy B Design

This is a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥12 years of age to ≤30 years of age who have received 2 or 3 doses of BNT162b2 (30-µg doses) with their last dose at least 4 months (120 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at Visit 1 and the alternative at Visit 3, four weeks later. Randomization will be stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Approximately 1500 participants will be randomized in the study. A blood sample will be collected to obtain a serum sample for troponin testing before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration.

Substudy C Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg and at 30 µg. Participants ≥12 years of age who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months (150 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive BNT162b2 at either a 10-µg or 30-µg dose level at Visit 301. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results at 7 days after the third dose. A DMC will review safety (e-diary and AE) and immunogenicity data in the first approximately 100 participants with available immunogenicity data in each age group (~50 participants in each dose level) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of the next age group will occur independently.

Total Number of Participants by Age Group and Dose Level

Age Group	Dose Level	Total Number of Participants per Dose Level	Total Number of Participants per Age Group
12-17 Years	10 µg, 30 µg	300	600
18-30 Years	10 µg, 30 µg	300	600
31-55 Years	10 µg, 30 µg	300	600
≥56 Years	10 µg, 30 µg	300	600

Up to 2400 participants will be randomized in the study.

Substudy D Design

This is a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose primary series of BNT162b2 OMI, and as a booster (third or fourth) dose at investigator sites in the US and South Africa only. Participants ≥18 years of age to ≤55 years of age will be enrolled. Approximately 1420 participants will be enrolled in the study.

Participants in Cohort 1 will have completed a 2-dose primary series of BNT162b2 (30-µg doses), with their last dose 90 to 240 days prior to enrollment. Approximately 615 participants will be randomized at a ratio of 1:1:1 either to receive 1 dose (third) of BNT162b2 OMI, 2 doses (third and fourth) of BNT162b2 OMI, 4 weeks apart, or 1 dose (third) of BNT162b2. Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose, but the investigator and sponsor will not be blinded.

Participants in Cohort 2 will be enrolled from Study C4591001 and C4591031 Substudy A and will have completed a 2-dose primary series and received a single booster (third) dose of BNT162b2, with their last dose 90 to 180 days prior to randomization. Approximately 600 participants will be randomized at a ratio of 1:1 to receive a fourth dose of either BNT162b2 or BNT162b2 OMI at Visit 401. Participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Cohort 2 will be observer-blinded.

In Cohort 3, 205 participants 18 through 55 years of age who are COVID-19 vaccine–naïve and have not experienced COVID-19 will be enrolled to receive 2 doses (primary series) of BNT162b2 OMI, 3 weeks apart, with a dose of BNT162b2 approximately 5 months (150 days) later. If participants do not consent to receive BNT162b2 as a third dose, they will not receive a third dose. No participants should receive BNT162b2 OMI as a third dose.

Table 1 details the number of participants by cohort and group, their prior BNT162b2 experience, the vaccine that will be administered, and the number of doses administered as part of Substudy D.

Table 1. Total Number of Participants by Cohort

Cohort	Group	Prior BNT162b2 Experience	Vaccine	Number of Doses Administered as Part of Substudy D	Total Number of Participants
Cohort 1	Group 1	2 Doses	BNT162b2 OMI	1	205
	Group 2	2 Doses	BNT162b2 OMI	2	205
	Group 2b	2 Doses	BNT162b2	1	205
Cohort 2	Group 3	3 Doses	BNT162b2 OMI	1 or 2	300
	Group 4	3 Doses	BNT162b2 (and BNT162b2 OMI at Visit 404)	1 or 2	300
Cohort 3	Group 5	Naïve	BNT162b2 OMI	2	205
			BNT162b2	1	

Note: Cohorts 1 and 2 are observer-blinded. Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose. Cohort 2 participants will be unblinded once they have completed Visit 404. Cohort 3 is open-labeled.

Substudy E Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose). Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses) with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization, will be enrolled at investigator sites in the US only. Participants >55 years of age will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 601 as a fourth dose. Participants 18 to 55 years of age will be randomized to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or BNT162b2 OMI at 60 µg at Visit 601 as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open-label) of 20 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 90 sentinel-cohort participants. An IRC will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 300 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

For participants 18 to 55 years of age, sentinel cohorts (sponsor open-label) of 30 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 15 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 75 sentinel-cohort participants. An IRC will review all reported AEs, reactogenicity e-diary data, and troponin levels from the sentinel cohorts collected through Day 7 to allow expanded enrollment upon confirmation of an acceptable safety assessment. An additional 900 participants will be enrolled and randomized in a 3:1:2 ratio to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg.

Substudy F Design

This is a randomized, observer-blinded substudy to describe the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose. Approximately 180 participants ≥60 years of age who have received 3 prior doses of BNT162b2 (30 µg doses), with the most recent dose being ≥4 months prior to randomization, will be enrolled in Israel. Participants will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 701 as a fourth dose.

Initially, sentinel cohorts (sponsor open-label) of 5 participants per group will be enrolled. An IRC and site representatives will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 25 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

Number of Participants

Substudy A will include 10,000 participants.

Substudy B will include up to 1500 participants.

Substudy C will include up to 2400 participants.

Substudy D will include up to 1420 participants.

Substudy E will include up to 2910 participants.

Substudy F will include up to 180 participants.

Data Monitoring Committee or Other Independent Oversight Committee

An external DMC will be formed and will review cumulative unblinded data throughout the study.

Substudy C will utilize a DMC that will be used to review safety and immunogenicity data in the first approximately 100 participants with available immunogenicity data in each age group (~50 participants in each dose level of BNT162b2) to guide age escalation.

Substudies E and F will utilize an IRC that will be used to review all reported AEs and reactogenicity data collected through Day 7 from all participants enrolled in the sentinel cohorts to evaluate if enrollment can be expanded in each group.

Statistical Methods:

The statistical methods will be specified in the respective substudy appendices.

1.2. Schema

Please refer to the appendices for the schema of each substudy.

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.

Refer to the SoA for Substudy A in Section 10.7.1.3, for Substudy B in Section 10.8.1.3, for Substudy C in Section 10.9.1.3, Substudy D in Section 10.10.1.3, Substudy E in Section 10.11.1.3 and Substudy F in Section 10.12.1.3.

2. INTRODUCTION

BNT162b2 is an RNA-based COVID-19 vaccine that is currently being investigated for the prevention of COVID-19 in individuals ≥6 months of age. On 02 December 2020, the MHRA in the UK granted a temporary authorization.[1] On 11 December 2020, the US FDA issued an EUA for use in individuals 16 years of age and older. BNT162b2 has now been granted a conditional marketing authorization, EUA, or temporary authorization in a total of more than 60 countries[2,3,4] and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 August 2021.[5]

2.1. Study Rationale

Like other COVID-19 vaccines recently developed, the long-term persistence of immunity and efficacy of BNT162b2 has yet to be studied. In addition, genetic lineages of SARS-CoV-2 have been emerging and circulating around the world since the beginning of the COVID-19 pandemic. There have been at least 12 different variants identified since December 2020. Within the first 3 months of the start of this global pandemic, the Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), and Epsilon (B.1.427 and B.1.429) variants were identified as VOCs. This is defined as a variant for which there is evidence of an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatment or vaccines, or diagnostic detection failures. On 21 September 2021, these variants were downgraded to variants being monitored. However, current VOCs include Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages). Delta, which has increased transmissibility, has dominated the number of infections in the latter half of 2021. Since the Omicron variant has been newly identified at the time of this protocol amendment, additional information will be learned as time progresses.[6]

A 2-dose series of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older after a median follow-up period of 2 months after the second dose.[7] However, as presented in April 2021, the efficacy of BNT162b2 from 7 days through up to 6 months after the second dose had decreased to 91.3% effective against COVID-19. However, the vaccine was 100% effective against severe disease as defined by the US CDC,

and 95.3% effective against severe COVID-19 as defined by the FDA.[8] Recent data from interim analysis of C4591031 Substudy A have demonstrated that a booster dose administered to individuals who previously received a primary 2-dose series of BNT162b2 restored vaccine protection against COVID-19 to the high levels achieved after the second dose, showing a relative VE of 95.6% when compared to those who did not receive the booster.[9] However, the efficacy of BNT162b2 in the face of recurring emergence of new SARS-CoV-2 variants, with multiple mutations in the S protein, is unknown. Therefore, the substudies within this master protocol will evaluate the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (eg, age groups) having previously received 2 doses of BNT162b2 administered 21 days apart, with the details and rationale for each strategy provided in the substudy appendices (Section 10.7 through Section 10.12).

Studying boosting strategies under a single master protocol, rather than separate protocols, will allow an organized approach that can be easily adapted as data emerge that can impact our understanding of what boosting strategies may be required. This approach will not only be more expeditious to implement, which is critical given the public health emergency the COVID-19 global pandemic represents, but also more readily understandable for investigational sites.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that 2019-nCoV was the underlying cause. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020.[10] On 11 February 2020, the virus was officially named as SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19.[10,11] SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, and on 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[12] To-date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died, demonstrating an urgent need for efficacious vaccines.[13]

Numerous COVID-19 vaccines are currently in development globally, and several candidate COVID-19 vaccines (eg, mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical studies and are now available under temporary or emergency authorizations.[14] BNT162b2, an RNA-based COVID-19 vaccine given as a 2-dose series administered 21 days apart, was shown to be safe and effective in a Phase 1/2/3 study and has received authorizations for temporary or emergency use or marketing authorizations in multiple countries and has been fully licensed for use in individuals 16 years of age and above in the US as of 23 August 2021.[5,15]

Recent evolution of SARS-CoV-2 is resulting in an emergence of new virus variants with multiple mutations in the S protein, which might be associated with the lower efficacy of some of the current vaccines. Therefore, there is a need to continue research including new approaches, such as evaluation of booster doses, to overcome waning immunity and/or the development of modified vaccines.[16]

Substudy B

Myocarditis and pericarditis are inflammatory conditions of the myocardium and the pericardium, respectively. A definitive diagnosis of myocarditis requires histological or immunohistological confirmation of an endomyocardial biopsy or other tissue specimen (eg, from an autopsy). Because of their invasive nature, biopsies are rarely obtained, and therefore a diagnosis of myocarditis is often based upon a compatible clinical scenario associated with noninvasive biomarker and imaging features.[17] This results in case definitions that are very complex, potentially based on multiple parameters (eg, Brighton Collaboration definitions).[18]

Abnormal ECG, echocardiogram, or troponin findings consistent with myocarditis with no cardiac symptoms have been reported in association with SARS-CoV-2 infection[19] but are not well characterized phenomena, and there is no widely accepted definition of subclinical myocarditis.

Substudy C

The results from 306 18- to 55-year-old participants from the C4591001 study who received a third (booster) dose of BNT162b2 30 µg a median of 6.8 months after their second dose demonstrated a strong immune response. The geometric mean neutralizing antibody titers against the reference strain were more than 3 times higher 1 month after the booster dose compared to 1 month after Dose 2.[20] Immunogenicity of the primary series in participants 12 to 15 of age was shown to be greater than in participants 16 to 25 years of age.[21] Further, a lower dose may produce a more favorable reactogenicity profile, with the additional benefit that it could improve vaccine accessibility by making more doses available. Therefore, the assessment of a 10-µg booster dose in individuals ≥12 years of age who have received the authorized 30-µg 2-dose primary series warrants further investigation.

Substudy D

On 24 November 2021, South Africa reported the identification of a new SARS-CoV-2 variant, B.1.1.529, to the WHO; the new variant has been named Omicron and has now been detected globally. The Omicron variant has many concerning spike protein mutations, some of which are known from other variants to be associated with reduced neutralization by convalescent and vaccinee sera. In regard to transmissibility, it is currently clear that Omicron spreads more efficiently from person to person.[22] However, it is unclear if infection with Omicron is associated with more severe disease.[23] Lastly, preliminary data announced on 08 December 2021 from an initial laboratory study demonstrated that serum antibodies induced by BNT162b2 neutralize the SARS-CoV-2 Omicron variant after 3 doses. Sera obtained from vaccinees 1 month after receiving the booster vaccination (third dose of BNT162b2) neutralized the Omicron variant to levels that are comparable to those observed for the wild-type SARS-CoV-2 spike protein after 2 doses. A third dose also strongly increases $CD8^+$ T-cell levels against multiple spike protein epitopes, which are considered to correlate with the protection against severe disease. Compared to the wild-type virus, the vast

majority of these epitopes remain unchanged in the Omicron spike variant.[24] Therefore, Substudy D has been designed to assess an Omicron-specific vaccine clinically.

Substudies E and F

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, was identified on 24 November 2021. As of 08 January 2022, it is now the dominant variant within the US, identified in 98.3% of sequenced COVID-19 cases.[25] It is currently unknown whether a single booster dose of BNT162b2, which has previously been demonstrated to have 95% clinical efficacy against SARS-CoV-2 (Delta being the dominant variant), will be as effective against the Omicron variant.

Data published on 31 December 2021 from the UK consisted of 2 studies examining the association between both variant and vaccination status and risk of hospitalization. Study 1 assessed the risk of hospitalization, and Study 2 assessed vaccine effectiveness against symptomatic infection and hospitalization. The results for Study 1 noted that the risk of hospitalization was lower for Omicron cases after 2 and 3 doses of vaccine, with an 81% (77%-85%) reduction in the risk of hospitalization after 3 doses compared to unvaccinated Omicron cases. With regard to Study 2, the vaccine effectiveness against hospitalization was 88% (78%-93%) for Omicron cases after 3 doses of vaccine.[26]

A recent laboratory study compared the neutralization of Omicron-infected cells in serum samples obtained from participants who had received 2 doses of BNT162b2 with neutralization in samples obtained from participants who had received 3 doses of BNT162b2. The neutralization efficiency of the BNT162b2 vaccine was also tested against wild-type SARS-CoV-2 and the Beta, Delta, and Omicron variants. The importance of a third vaccine dose was evidenced by a higher neutralization efficiency (by a factor of 100) against the Omicron variant after the third dose than after the second dose. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.[27] Therefore, the addition of a higher-dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile. Therefore, Substudies E and F have been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

2.2.1. Clinical Overview

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~46,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate.[7] The trial is being conducted in a heterogeneous study population: eligible participants ≥12 years of age, healthy participants, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. The study consists of 2 parts: Phase 1: to identify the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg

[for BNT162b1]); Phase 2/3: an expanded-cohort and efficacy part for the selected vaccine candidate (BNT162b2).

The available immunogenicity data from Phase 1 participants show that BNT162b2 induced a robust IgG-binding response to S1 and a SARS-CoV-2–neutralizing response. Immunogenicity substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response. BNT162b2 was selected from the Phase 1 part of the study based on the overall safety, tolerability, and immunogenicity. In a mid-November 2020 analysis of 36,621 participants randomized 1:1 to vaccine or placebo, who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination schedule, the efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the active vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.[28]

In a subsequent analysis of 927 confirmed symptomatic cases of COVID-19, an efficacy rate of 91.3% was observed for BNT162b2 in preventing such cases occurring between 7 days to 6 months after the second dose.[29] Furthermore, from the same analysis, BNT162b2 was shown to have an efficacy of:

- 100% in preventing severe disease as defined by the CDC.
- 95.3% in preventing severe disease as defined by the FDA.
- 100% in preventing COVID-19 cases in South Africa, where the B.1.351 lineage is prevalent.

Safety data from approximately 38,000 participants at least 16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose demonstrated a favorable safety profile. Available safety data from all participants enrolled through the 14 November 2020 data cutoff (N=43,252, which includes late enrollment of additional adolescent and adult participants) were consistent with the safety profile for the approximately 38,000 participants with a median follow-up of 2 months and also did not raise specific safety concerns.[28]

The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants

≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). The frequency of SAEs was low (<0.5%), without meaningful imbalances between study arms. Lymphadenopathy was observed in 0.3% of vaccine recipients as compared to <0.1% of those who received placebo. Otherwise, there were no notable patterns or numerical imbalances between vaccine groups for specific categories of nonserious AEs (including other neurologic, neuroinflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, sexes, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.[28]

On 22 September 2021, based on safety and immunogenicity data from approximately 300 immunocompetent adult booster dose recipients from Study C4591001, the FDA issued the EUA for a single booster dose of BNT162b2 30 µg for 1) individuals 65 years of age and older; 2) individuals 18 through 64 years of age at high risk of severe COVID-19; and 3) individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.[30] On 19 November 2021, the FDA amended the EUA, authorizing use of a single booster dose for all individuals 18 years of age and older after completion of primary vaccination with an FDA-approved COVID-19 vaccine.[31] On 09 December 2021, the FDA again amended the EUA to authorize the use of a single booster dose for administration to individuals 16 and 17 years of age at least 6 months after completion of primary vaccination with BNT162b2.[32] In addition, a booster dose of the vaccine is authorized in the EU and other countries, with recommendations for populations varying based on local health authority guidance.[33,34]

The per-protocol interim safety and efficacy analysis was conducted in October 2021 for Study C4591031 Substudy A. In this study, approximately 10,000 participants who had previously received 2 doses of BNT162b2 as a primary series in Study C4591001 were randomized 1:1 in Study C4591031 to receive either a 30-µg booster dose (the same dosage strength as in the 2-dose primary series) or placebo. The time between the second dose and administration of the booster dose or placebo for most participants was ≥10 to <12 months.

Symptomatic COVID-19 occurrence was measured from ≥7 days after booster or placebo, with a median follow-up of 2.5 months. During the blinded placebo-controlled study period up to a data cutoff date of 05 October 2021, there were a total of 6 cases of COVID-19 in the booster group, and 123 cases in the nonboosted placebo group, in the evaluable efficacy population without evidence of prior SARS-CoV-2 infection. The observed relative VE was 95.3% (2-sided 95% CI: 89.5%, 98.3%), which reflects the reduction in disease occurrence in the boosted group versus the nonboosted group. The AE profile was generally consistent with other previously submitted clinical safety data for the vaccine, with no new safety concerns identified. No cases of myocarditis or pericarditis were reported.[35]

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no approved or licensed preventive or therapeutic options available. However, based on the data available from the C4591001 study, multiple temporary or EUAs have been granted. The available safety and immunogenicity data from the ongoing Pfizer-BioNTech clinical trial combined with available nonclinical data with BNT162 vaccines and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable benefit/risk profile and support continued clinical development of BNT162b2.

In the C4591001 study, BNT162b2 has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%).[28] Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of participants reporting hypersensitivity-related AEs was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs 111 [0.51%]). Severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in older adults (>55 years of age) (≤2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited AEs, lymphadenopathy occurred much more frequently in the active vaccine group than the placebo group and is plausibly related to vaccination. SAEs, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study.[28]

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. The risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of VAED.[28]

In the latest analysis from C4591001, vaccine safety has been evaluated in more than 44,000 participants ≥16 years of age, with more than 12,000 vaccinated participants having at least 6 months follow-up after their second dose. No serious safety concerns have been observed in this timeframe. Side effects observed in this analysis were generally consistent with previously reported results.[29]

Continued clinical investigation is justified, given:

- the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection.
- the potential of the BioNTech platform of RNA-based vaccines to deliver high numbers of vaccine doses rapidly in a single production campaign.
- the threat posed by the SARS-CoV-2 variants emerging worldwide.

- the potential need for enhancing immunoresponses to overcome waning immunity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 RNA-Based COVID-19 Vaccine		
Local reactions and systemic events may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine. The most common events reported in Study C4591001 were mild to moderate pain at the injection site, fatigue, and headache.[28]	• Local reactions and systemic events will be recorded as AEs or captured in an e-diary (in Substudies B, C, D, E, and F). • All study participants will be observed for at least 30 minutes after vaccination. • Given that higher dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI will be administered in Substudies E and F, these substudies will include review of e-diary data reported through Day 7 from sentinel cohorts of 20 participants per group in Substudy E and 5 participants per group in Substudy F by an IRC before expanding enrollment. See Sections 10.11.4.1 and 10.12.4.1 for details.
Safety profile of a novel vaccine not yet fully characterized. Adverse reactions (risks) identified from the postauthorization safety data include the following: anaphylaxis, other hypersensitivity reactions (eg, rash, pruritus, urticaria, angioedema), pain in extremity (injected arm), vomiting, and diarrhea.	Data available from the C4591001 study showed low incidence of severe or serious events and no clinically concerning safety observations across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.[28] Postauthorization safety data surveillance has confirmed the safety profile observed in C4591001 and has resulted in identification of some additional adverse reactions (risks) as noted in this table.	• Collection of AEs from signing of the ICD through 1 month after the booster or last study vaccination. • Collection of SAEs from signing of the ICD through 6 months after the booster or last study vaccination. • DMC review throughout the study to review all safety data. • All participants will be observed for at least 30 minutes after vaccination. • Given that higher dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI will be administered in Substudies E

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		and F, these substudies will include review of AE data reported through Day 7 from sentinel cohorts of 20 participants per group in Substudy E and 5 participants per group in Substudy F by an IRC before expanding enrollment. See Sections 10.11.4.1 and 10.12.4.1 for details.
Theoretical risk for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with RSV, feline coronavirus, and Dengue virus vaccines. It is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection. No evidence of disease enhancement has been seen in large-scale clinical study of BNT162b2 in humans or in postauthorization surveillance.	Monitoring for cases of COVID-19 developing during the study, which will be reported at COVID-19 illness visits for substudies that include those visits or as AESIs for those substudies that do not. Assessments of individual cases for disease enhancement is challenging based on current understanding of mechanism of pathogenesis, thus evaluations of any adverse or unexpected imbalances in severe COVID-19 cases may provide insight to a potential signal for this theoretical risk.
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: The estimated rate is 5.0 per million doses administered. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 10.7.8.5.9 for Substudy A, Section 10.8.8.3.6 for Substudy B, Section 10.9.8.5 for Substudy C, Section 10.10.8.6.7 for Substudy D, Section 10.11.8.6.12 for Substudy E, and Section 10.12.8.5.10 for Substudy F.

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	• Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. • Monitoring for cases of COVID-19 developing during the study, which will be reported as AESIs.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled in Substudy A are detailed in Section 10.7.2.3.1, for Substudy B in Section 10.8.2.3.1, for Substudy C in Section 10.9.2.2.1, Substudy D in Section 10.10.2.2.1, for Substudy E in Section 10.11.2.2.1, and for Substudy F in Section 10.12.2.2.1.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risks to participants participating in each substudy, the potential risks identified in association with BNT162b2 are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

For substudy-specific objectives and endpoints, refer to each respective substudy appendix.

For Substudy A, refer to Section 10.7.3.

For Substudy B, refer to Section 10.8.3.

For Substudy C, refer to Section 10.9.3.

For Substudy D, refer to Section 10.10.3.

For Substudy E, refer to Section 10.11.3.

For Substudy F, refer to Section 10.12.3.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed in Section 10.7 through Section 10.12. Each substudy may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the master protocol study rationale.

See the substudy appendices for the rationales supporting each substudy.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for BNT162b2, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4) if indicated by the substudy eligibility criteria.

4.3. Justification for Dose

Based on data from the Phase 1 component of clinical trial C4591001 and available nonclinical data, the modRNA BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2/3 evaluation of safety, immunogenicity, and efficacy after 2 doses administered 3 weeks apart. This is the dose that was shown to be effective and has been approved in multiple countries worldwide.

The vaccine candidate BNT162b1 was initially studied in clinical trial C4591001, but BNT162b2 was selected for Phase 2/3 development due to its better tolerability profile.[36] While the 30-µg dose level of BNT162b2 was advanced, higher dose levels of BNT162b1 (50 µg, 60 µg, and 100 µg) were studied in 18- to 55-year-old participants.[37,38] Due to the level of reactogenicity observed, these dose levels were not advanced. The Phase 2/3 part of clinical trial C4591001 demonstrated that systemic reactogenicity was higher in 16- to 55-year-olds compared to those older than 55 years of age.[7] In light of better tolerability in older adults, the waning of efficacy observed, and the immune escape exhibited by the Omicron variant, study of a higher dose of the vaccine is warranted.

For Substudies E and F, high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2, given as a fourth dose, will be evaluated. BNT162b2 at a dose of 30 µg will be used as a control in Substudies E and F.

4.4. End of Study Definition

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

A participant is considered to have completed the (sub)study if he/she has completed all phases of the (sub)study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreener for study recruitment purposes will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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 substudy-specific inclusion criteria are met.

For Substudy A, see Section 10.7.5.1.

For Substudy B, see Section 10.8.5.1.

For Substudy C, see Section 10.9.5.1.

For Substudy D, see Section 10.10.5.1.

For Substudy E, see Section 10.11.5.1.

For Substudy F, see Section 10.12.5.1.

Some inclusion criteria are common to all substudies: participants (and their parent[s]/legal guardian[s]) willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures; participants should be healthy; and participants (or their parent[s]/legal guardian[s]) must be capable of giving personal signed informed consent.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the substudy-specific exclusion criteria apply.

Some exclusion criteria are common to all substudies: participants with medical or psychiatric conditions that may increase the risk of study participation; history of severe adverse reactions associated with a vaccine and/or severe allergic reaction to any component of the study vaccination; previous clinical or microbiological diagnosis of COVID-19; immunocompromised individuals; or participants with bleeding diathesis.

For Substudy A, see Section 10.7.5.2.

For Substudy B, see Section 10.8.5.2.

For Substudy C, see Section 10.9.5.2.

For Substudy D, see Section 10.10.5.2.

For Substudy E, see Section 10.11.5.2.

For Substudy F, see Section 10.12.5.2.

5.3. Lifestyle Considerations

5.3.1. Contraception

The following section is applicable if indicated by the substudy eligibility criteria.

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) considering that their risk for pregnancy may have changed since the last visit. 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 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 SAEs.

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/Administration of Study Intervention

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. Participants meeting these criteria at Vaccination 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

- Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
- Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
- Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
- 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. SPECIFIC STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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.

6.1. Study Intervention(s) Administered

For the purposes of the master protocol, study intervention refers to the 30 µg dose level of BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S). Additional study intervention(s) are detailed for each substudy, if applicable. Additional study interventions administered in Substudy A are detailed in Section 10.7.6, Substudy B in Section 10.8.6, Substudy C in Section 10.9.6, Substudy D in Section 10.10.6, Substudy E in Section 10.11.6, and Substudy F in Section 10.12.6.

Intervention Name	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	30-µg
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP	IMP
Sourcing	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

6.1.1. Administration

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.

See Section 10.7.6.1.1 for further study intervention administration details for Substudy A.

See Section 10.8.6.1.1 for further study intervention administration details for Substudy B.

See Section 10.9.6.1.1 for further study intervention administration details for Substudy C.

See Section 10.10.6.1.1 for further study intervention administration details for Substudy D.

See Section 10.11.6.1.1 for further study intervention administration details for Substudy E.

See Section 10.12.6.1.1 for further study intervention administration details for Substudy F.

6.2. Preparation, Handling, Storage, and 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 once diluted.

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 preparation and dispensing.

See Section 10.7.6.1.2 for additional preparation and dispensing details for Substudy A.

See Section 10.8.6.1.2 for additional preparation and dispensing details for Substudy B.

See Section 10.9.6.1.2 for additional preparation and dispensing details for Substudy C.

See Section 10.10.6.1.2 for additional preparation and dispensing details for Substudy D.

See Section 10.11.6.1.2 for additional preparation and dispensing details for Substudy E.

See Section 10.12.6.1.2 for additional preparation and dispensing details for Substudy F.

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 using 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.

Study intervention will be dispensed at the study visits summarized in the SoA.

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 Arrangements

Blinding arrangements for site personnel and the sponsor for Substudy A are detailed in Section 10.7.6.2.1 and Section 10.7.6.2.2.

Blinding arrangements for site personnel and the sponsor for Substudy B are detailed in Section 10.8.6.2.1 and Section 10.8.6.2.2.

Blinding arrangements for site personnel and the sponsor for Substudy C are detailed in Section 10.9.6.2.1 and Section 10.9.6.2.2.

Blinding arrangements for site personnel and the sponsor for Substudy D are detailed in Section 10.10.6.2.1 and Section 10.10.6.2.2.

Blinding arrangements for site personnel and the sponsor for Substudy E are detailed in Section 10.11.6.2.1 and Section 10.11.6.2.2.

Blinding arrangements for site personnel and the sponsor for Substudy F are detailed in Section 10.12.6.2.1 and Section 10.12.6.2.2.

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. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention After the End of the Study

For Substudies A, B, D, E, and F, no intervention will be provided to study participants at the end of their study participation.

For Substudy C, if the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose.

6.7. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer 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.

6.8. Concomitant Therapy

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

- Any vaccinations received from 28 days prior to study enrollment until 28 days following administration of the last study intervention.
- Prohibited medications listed in Section 6.8.1 will be recorded to include start and stop dates, name of the medication, dose, unit, route, and frequency.

6.8.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per 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 through 28 days after administration of the last study intervention.
- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 within 90 days before enrollment through conclusion of the study.
- Receipt of any other (nonstudy) coronavirus vaccine at any time 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.

6.8.2. Permitted During the Study

Medication other than that described as prohibited in Section 6.8.1 required for treatment of preexisting conditions or acute illness is permitted.

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

Hormonal contraceptives that meet the requirements of this study can be used in participants who are WOCBP (see Appendix 4).

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. Reasons for permanent discontinuation of study intervention 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*).

*A positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. If study intervention (other than Dose 1) has been delayed per Section 5.5, because of febrile or other acute illness (Item 1 in the Section 5.5 list), and the investigator later diagnoses the signs and symptoms as COVID-19 (with or without a positive SARS-CoV-2 NAAT result), the participant may receive a further dose of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and immunogenicity. 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. Participants who remain in the study for evaluation of safety will be contacted by telephone 6 months after their last study vaccination to record AEs as described in Section 8.3.

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 include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant or parent/legal guardian request;
- Investigator request;
- Protocol deviation (Note: from site receipt of a PACL dated 21 September 2021, receipt of a nonstudy COVID-19 vaccine during study participation will result in study withdrawal).

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.

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.

If a participant has previously withdrawn consent and wishes to receive a COVID-19 vaccine outside the study, he or she may request to know which study intervention he or she received at Visit 1 without needing to reconsent.

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. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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

See Section 10.7.8 for assessments and procedures specific to Substudy A, Section 10.8.8 for Substudy B, Section 10.9.8 for Substudy C, Section 10.10.8 for Substudy D, Section 10.11.8 for Substudy E, and Section 10.12.8 for Substudy F.

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

The 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.

8.1. Efficacy Assessments and/or Immunogenicity Assessments

Serum samples may be obtained for immunogenicity testing at the visits specified in the substudy SoA and assays performed as detailed for each substudy.

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 (and by the site [Sheba] and BioNTech for Substudy F). 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 vaccines or vaccine-related products, and/or for vaccine related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

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 genetic material is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

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 their 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 30 minutes after administration of the study intervention will be assessed and documented in the AE CRF.

For Substudies B, C, D, E, and F:

The safety parameters also include reactogenicity e-diary reports of local reactions, 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 8.2.4.

8.2.1. Physical Examinations

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to Section 8.3.3.

8.2.2. Vital Signs

The participant's body temperature will be measured prior to each vaccination.

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.2.4. Electronic Diary – Applicable Only to Substudies B, C, D, E, and F

Participants will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the participant's own personal device. All participants will be asked to monitor and record local reactions, systemic events, and

antipyretic medication usage for 7 days from the day of 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. Generally, 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.

8.2.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[39]

8.2.4.2. 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 to 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[a])
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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the case report form.

8.2.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue/tiredness, 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

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as an AE rather than as systemic events in the reactogenicity e-diary.

Potential COVID-19 symptoms that do not overlap with systemic events should be reported as AEs as per Section 8.3.

8.2.4.4. 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. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 4 during analysis.

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)

8.2.4.5. Antipyretic/Analgesic Medication

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

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, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

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).

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

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

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

For all participants, information about AEs will be collected for events occurring within approximately 1 month after each vaccination, and information about SAEs will be collected for events occurring approximately 6 months after each vaccination.

Substudy A

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2, and from Visit 101 to Visit 102.

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to Visit 3 (approximately 6 months after the booster vaccination), and from Visit 101 to 103 (approximately 6 months after participants who originally received placebo are administered BNT162b2).

Substudy B

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 205 (1 month after Vaccination 2).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

Substudy C

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 303 (1 month after the third dose).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to Visit 304 (approximately 6 months after the participant's last study vaccination).

Substudy D

For Cohorts 1 and 2, 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 402 (1 month after the participant's study vaccination) for Groups 1, 2b, 3, and 4, through and including Visit 403 for Group 2, and from Visit 404 through and including Visit 404b for Group 3 and Group 4 participants who receive a dose of BNT162b2 OMI at Visit 404.

For Group 5, 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 504 (1 month after the participant's second study vaccination), and from Visit 506 through Visit 507 (1 month after the participant's third study vaccination).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent through Visit 405 for Groups 1 to 4, and Visit 508 for Group 5 (approximately 6 months after the participant's last study vaccination).

Substudy E

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 603 (1 month after the participant's study vaccination).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to Visit 605 (approximately 6 months after the participant's study vaccination).

Substudy F

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 703 (1 month after the participant's study vaccination).

In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to Visit 705 (approximately 6 months after the participant's study vaccination).

For all 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.

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 permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

After the initial AE or 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 toward 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. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study 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 EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.
- The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).
- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting 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 28 days after the last dose of study intervention. Beyond 28 days after the last dose of study intervention, any pregnancy that occurs will not be considered EDP for this study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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

integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

8.3.7.1. Substudies Including a Potential COVID-19 Illness Visit

The following substudies include a potential COVID-19 illness visit: Substudies A, D, E, and F.

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

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

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

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

OR

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

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

8.3.7.2. Substudies NOT Including a Potential COVID-19 Illness Visit

For substudies not including a potential COVID-19 illness visit, confirmed COVID-19 diagnoses will be considered AESIs (Section 8.3.8).

8.3.8. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 10.7.8.5.9 for Substudy A, Section 10.8.8.3.6 for Substudy B, Section 10.9.8.5 for Substudy C, Section 10.10.8.6.7 for Substudy D, Section 10.11.8.6.12 for Substudy E, and Section 10.12.8.5.10 for Substudy F for additional procedures for monitoring of potential myocarditis or pericarditis.

8.3.8.1. Substudies NOT Including a Potential COVID-19 Illness Visit

This section provides information on AESIs that may be detected during the study:

- Confirmed COVID-19 diagnosis (clinical signs/symptoms and positive SARS-CoV-2 NAAT test)

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.3.8.2. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

8.5.1. Specified Genetics

For Substudies A, B, C, and F, genetics (specified analyses) are not evaluated.

For Substudies D and E, please see Section 10.16.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Statistical Hypotheses

9.1.1. Estimands

For estimands, refer to the respective appendix for each substudy. For Substudy A, refer to Section 10.7.3. For Substudy B, refer to Section 10.8.3. For Substudy C, refer to Section 10.9.3. For Substudy D, refer to Section 10.10.3. For Substudy E, refer to Section 10.11.3. For Substudy F, refer to Section 10.12.3.

9.1.2. Statistical Hypotheses

For Substudy A, refer to Section 10.7.9.1.2 for hypotheses.

For Substudy B, refer to Section 10.8.9.1.2 for hypotheses.

For Substudy C, refer to Section 10.9.9.1.2 for hypotheses.

For Substudy D, refer to Section 10.10.9.1.2 for hypotheses.

For Substudy E, refer to Section 10.11.9.1.2 for hypotheses.

For Substudy F, refer to Section 10.12.9.1.2 for hypotheses.

9.1.3. Multiplicity Adjustments

For Substudy A, refer to Section 10.7.9.1.3 for multiplicity adjustments.

For Substudy B, refer to Section 10.8.9.1.3 for multiplicity adjustments.

For Substudy C, refer to Section 10.9.9.1.3 for multiplicity adjustments.

For Substudy D, refer to Section 10.10.9.1.3 for multiplicity adjustments.

For Substudy E, refer to Section 10.11.9.1.3 for multiplicity adjustments.

For Substudy F, refer to Section 10.12.9.1.3 for multiplicity adjustments.

9.2. Analysis Sets

For analysis sets, refer to the respective appendix for each substudy.

For Substudy A, refer to Section 10.7.9.2.

For Substudy B, refer to Section 10.8.9.2.

For Substudy C, refer to Section 10.9.9.2.

For Substudy D, refer to Section 10.10.9.2.

For Substudy E, refer to Section 10.11.9.2.

For Substudy F, refer to Section 10.12.9.2.

9.3. Statistical Analyses

The SAP will be developed and finalized for each substudy before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the general considerations of statistical analyses.

Refer to each substudy appendix for description of the statistical analyses for primary, secondary, and/or exploratory endpoints. For Substudy A, refer to Section 10.7.9.3. For Substudy B, refer to Section 10.8.9.3. For Substudy C, refer to Section 10.9.9.3. For Substudy D, refer to Section 10.10.9.3. For Substudy E, refer to Section 10.11.9.3. For Substudy F, refer to Section 10.12.9.3.

9.3.1. General Considerations

Each substudy will be reported separately.

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the vaccine group to which they were randomized. Missing laboratory results will not be imputed.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method). The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.

The 3-tier approach may be used to summarize AEs for certain substudies (refer to each substudy for specification). For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

9.3.1.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

9.3.1.2.1. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

9.3.1.2.2. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

9.4. Interim Analyses

Interim analyses will be determined by substudy, and details are provided in each corresponding appendix as necessary.

9.5. Sample Size Determination

Sample size will be determined by substudy, and details are provided in each corresponding appendix.

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her parent(s)/legal guardian(s) and answer all questions regarding the study. The participant or his/her parent(s)/legal guardian(s) 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 or their parent(s)/legal guardian(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

When consent is obtained from a participant's parent(s)/legal guardian(s), the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC.

The investigator must ensure that each study participant or his/her parent(s)/legal guardian(s) 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 or his/her parent(s)/legal guardian(s) must be informed that the participant's 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 or his/her parent(s)/legal guardian(s).

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

The investigator further must ensure that each study participant or his/her parent(s)/legal guardian(s) 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 on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their parent(s)/legal guardian(s) must be reconsented to the most current version of the ICD(s) during the participant's participation in the study.

A copy of the ICD(s) must be provided to the participant or his/her parent(s)/legal guardian(s).

Participants who are rescreened are required to sign a new ICD.

10.1.4. 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 ID. 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee and Other Independent Oversight Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators, as appropriate.

Substudies E and F will also use an IRC that will be responsible for reviewing safety data as described in Sections 10.11.9.4.2 and 10.12.9.4.2.

Any further involvement of the DMC in each substudy is specified in the corresponding substudy appendix.

See Section 10.7.9.4.2 for details of the DMC's role in Substudy A.

See Section 10.8.9.4.1 for details of the DMC's role in Substudy B.

See Section 10.9.9.4.2 for details of the DMC's role in Substudy C.

See Section 10.10.9.4.2 for details of the DMC's role in Substudy D.

See Section 10.11.9.4.2 for details of the DMC's role in Substudy E.

See Section 10.12.9.4.2 for details of the DMC's role in Substudy F.

10.1.6. 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 data from these trials available 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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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 retain 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.

10.1.8. 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 and its origin can be found in the study monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the study monitoring plan, which is maintained by the sponsor.

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. 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/CRO 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 the ICH 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.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. 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/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

If required based on each substudy design and participant population, a pregnancy test will be performed at times defined in the SoA section of each substudy.

- Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for participants who are WOCBP.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Investigators must document their review of each laboratory safety report.

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 condition 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 or 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 that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

- The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs;

(2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting 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	All AEs or SAEs associated with exposure during pregnancy or breastfeeding Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or 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 or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or 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 or 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 or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However**, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting 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 submitted documents. • 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 an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

The following appendix applies as specified in each substudy eligibility criteria section.

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 contraception/barrier as detailed below:
- Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

3. Documented hysterectomy;

4. Documented bilateral salpingectomy;

5. 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.

- 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.

- A 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 (eg, bilateral tubal ligation).
5. Vasectomized partner:
   - A 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.
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 "adaptors" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure 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 Hy's law cases, 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, or 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, 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: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

10.6.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.7. Appendix 7: Substudy A

10.7.1. Substudy Summary

10.7.1.1. Synopsis

See Section 1.1 for a synopsis of Substudy A.

10.7.1.2. Schema

	Visit Number	1	2	3	4	Unplanned
	Visit Description	**Booster Vaccination**	**1-Month Telephone Contact**	**6-Month Follow-Up Visit**	**12-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Participants having received 2 prior doses of 30 µg BNT162b2 at least 6 months prior to randomization	Group 1 (n=5000)	BNT162b2				
	Group 2 (n=5000)	Placebo				
	Blood draw	20 mL		20 mL		

Visit Number	101	102	103	Unplanned
Visit Description	**BNT162b2 Vaccination**	**1-Month Telephone Contact 2**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Group 2	BNT162b2			
Blood Draw	20 mL			

10.7.1.3. Schedule of Activities for Substudy A

Visit Number	1	2	3	4	Unplanned
Visit Description	**Booster Vaccination**	**1-Month Telephone Contact**	**6-Month Follow-Up Visit[a]**	**12-Month Telephone Contact[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window	**Day 1[c]**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**350 to 378 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X				
Obtain the participant's prior participant number from Study C4591001	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment[d]	X				
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	X	
Measure height and weight	X				
Measure temperature (body)	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X	X			
Collect nonstudy vaccine information	X	X			
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity assessment	~20 mL		~20 mL		
Obtain nasal (midturbinate) swab	X				X
Obtain randomization number and study intervention allocation	X				
Administer study intervention	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Explain participant communication methods, assist the participant with downloading the app, or issue provisioned device, if required	X				

Visit Number	1	2	3	4	Unplanned
Visit Description	**Booster Vaccination**	**1-Month Telephone Contact**	**6-Month Follow-Up Visit[a]**	**12-Month Telephone Contact[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window	**Day 1[c]**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**350 to 378 Days After Visit 1**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Provide/ensure the participant has a thermometer	X				
Request the participant return the e-diary or assist the participant to delete the application				X	
Collect AEs and SAEs as appropriate	X	X	X[e]		X[f]
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)					X
Contact the participant by telephone		X		X	

a. This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined BNT162b2 booster vaccination.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
d. Including, if indicated, a physical examination.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
f. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

10.7.1.3.1. Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who originally received placebo will have the opportunity to receive BNT162b2 as part of the study either indicated by, and at a time informed by, the outcome of the interim analyses detailed in Section 10.7.9.4 or at a time decided at the discretion of the sponsor.

Visit Number	101	102	103	Unplanned
Visit Description	**BNT162b2 Vaccination**	**1-Month Telephone Contact 2**	**6-Month Telephone Contact**	**Potential COVID-19 Illness Visit**
Visit Window	**As Informed by the Outcome of the Interim Analyses, or at the Discretion of the Sponsor**	**28 to 35 Days After Visit 101**	**175 to 189 Days After Visit 101**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Confirm participant originally received placebo	X			
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X	X	
Perform urine pregnancy test (if appropriate)	X			
Confirm use of contraceptives (if appropriate)	X			
Collect prohibited medication use	X	X	X	X
Confirm eligibility	X			
Review temporary delay criteria	X			
Collect blood sample for immunogenicity assessment	~20 mL			
Obtain nasal (midturbinate) swab	X			X
Obtain vaccine vial allocation via IRT	X			
Administer BNT162b2	X			
Assess acute reactions for at least 30 minutes after study intervention administration	X			
Request the participant return the e-diary or assist the participant to delete the application			X	
Collect AEs and SAEs as appropriate	X	X	X	X[a]
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)				X
Contact the participant by telephone		X	X	

Abbreviations: HIV = human immunodeficiency virus; IRT = interactive response technology.
a. AEs need only be recorded if the participant remains in the AE reporting period (see Section 8.3.1).

10.7.2. Introduction

10.7.2.1. Study Rationale

Substudy A will evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2 when administered to participants having previously received 2 doses of BNT162b2 at least 6 months prior to randomization.

10.7.2.2. Background

See Section 2.2 for the study background.

10.7.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy A beyond those detailed for the master study (see Section 2.3).

10.7.2.3.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy A may be:

- Receipt of a booster dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Access to COVID-19 diagnostic testing.
- Contributing to research to help others in a time of global pandemic.

10.7.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Efficacy	**Primary Efficacy**	**Primary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose	• AEs • SAEs
Secondary Efficacy	**Secondary Efficacy**	**Secondary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
Exploratory		
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received the BNT162b2 booster dose	In participants who received BNT162b2 at the booster vaccination (at initial randomization or subsequently): Incidence per 1000 person-years of follow-up	Confirmed COVID-19 incidence per 1000 person-years of follow-up

10.7.4. Study Design

10.7.4.1. Overall Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo as shown in Section 10.7.1.2. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥16 to 55 years of age and approximately 40% of participants >55 years of age. Approximately 10,000 participants will be randomized in the study. Assuming a 15% nonevaluable rate, there will be approximately 4250 evaluable participants in each group.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses, as outlined below in Section 10.7.4.2.1 and further detailed in Section 10.7.9.4, or at the discretion of the sponsor. The timing of this booster vaccination may be informed by the outcome of the interim analyses detailed in Section 10.7.9.4 or at a time decided by the sponsor.

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

10.7.4.2. Scientific Rationale for Substudy A Design

See Section 10.7.2.1.

10.7.4.2.1. Statistical Rationale for Substudy A Design

In addition to assessing the safety of administering a booster dose in a large number of participants, a key objective of this study is to characterize the potential for waning VE over time in participants who do not receive a booster. It is important to identify when a booster is needed to protect the participants in this trial, as well as to inform vaccine policy decision-makers. Consequently, the most appropriate statistical framework to facilitate decision-making in this setting is periodic statistical summaries (every 2 months over the scheduled 6-month follow-up period) using statistical guidelines, rather than the traditional hypothesis testing framework with strong control of overall type 1 error across analysis time points.

Using a traditional hypothesis testing framework, a policy of recommending a booster would be implemented only if the lower limit of the alpha-adjusted CI for VE of the boosted group relative to the unboosted group was greater than some specified value (eg, 20% or 30%). This approach controls the overall type 1 error, that is, deciding that a booster is necessary to maintain VE when it is actually not necessary. But strong control of type 1 error inflates type

2 error for a fixed sample size. And in this setting, type 2 error, that is, deciding that a booster is not necessary when it actually is, has a greater negative impact on public health.

For this reason, a descriptive statistical approach will be used with point estimates of VE (boosted relative to unboosted) and unadjusted (for multiplicity) 95% CIs at each time point (2, 4, and 6 months). In addition, to help put these results into perspective, an inferred VE for the unboosted group (relative to an unvaccinated population) will be calculated. Specifically, assuming that the newly boosted group has the same VE (relative to an unvaccinated population) over time that was observed in the parent C4591001 trial, an inferred unvaccinated (placebo) disease rate can be obtained at various time points and used to calculate the inferred VE (relative to unvaccinated) for the unboosted group. If this value is lower than a specified value (eg, 60%) at a given analysis time point, then a decision to offer a booster to the unboosted participants at that time may be implemented.

10.7.4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics shown to reflect that achieved in C4591001.[40]

10.7.4.3. Justification for Dose

See Section 4.3 for a justification of the BNT162b2 dose used in Substudy A.

10.7.4.4. End of Study Definition

See Section 4.4.

10.7.5. Study Population

Details of the master eligibility criteria are shown in Section 5. Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy A–specific inclusion and exclusion criteria.

10.7.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥16 years of age at Visit 1 (Day 1) who participated in Study C4591001.

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

Type of Participant and Disease Characteristics:

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

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

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.15.

Informed Consent:

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

The investigator, or a person designated by the investigator, will obtain written/electronically signed informed consent (and assent) from each study participant's legal guardian (as defined in Appendix 1), and the participant's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

Other Inclusions:

5. Participants who have received 2 prior doses of 30 µg BNT162b2 19 to 42 days apart, with the second dose being at least 175 days before Visit 1 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

10.7.5.2. Exclusion Criteria

Participants are excluded from Substudy A 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. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

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

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

6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

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

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

12. Prior receipt of more than 2 doses of BNT162b2 30 µg.

13. Participation in other studies involving study intervention within 28 days prior to study entry, other than C4591001, and/or within 28 days of confirmed receipt of BNT162b2 within the study.

10.7.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy A as detailed in Section 5.3 and Section 10.4.

10.7.5.4. Screen Failures

See Section 5.4.

10.7.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.7.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

10.7.6.1. Study Intervention(s) Administered

See Section 6.1 for details of BNT162b2.

Additional Intervention Name	Saline Placebo
Type	Placebo
Dose Formulation	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	N/A
Dosage Level(s)	N/A
Route of Administration	Intramuscular injection
Use	Placebo
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	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

10.7.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 1 in accordance with the substudy's SoA (Section 10.7.1.3).

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

Study intervention administration at Visit 101 will be conducted in an open-label manner.

10.7.6.1.2. Preparation and Dispensing

For booster vaccination during Substudy A, study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants remain blinded.

10.7.6.2. Measures to Minimize Bias: Randomization and Blinding

10.7.6.2.1. Blinding of Site Personnel

In this observer-blinded substudy, 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 there are differences in physical appearance of the study interventions, the study intervention will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The study will be unblinded to site personnel at a time informed by the outcome of the interim analyses, as detailed in Section 10.7.9.4, or at a time decided by the sponsor.

10.7.6.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 10.7.9.4.2). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

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

- The study will be unblinded to all sponsor/Pfizer staff at a time informed by the outcome of the interim analyses, as detailed in Section 10.7.9.4, or at a time decided by the sponsor.

10.7.6.2.3. 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.

10.7.6.3. Study Intervention Compliance

See Section 6.4.

10.7.6.4. Dose Modification

See Section 6.5.

10.7.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.7.6.6. Treatment of Overdose

See Section 6.7.

10.7.6.7. Concomitant Therapy

See Section 6.8.

10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.7.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 60 mL.

For all participants, 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.

10.7.8.1. Efficacy and/or Immunogenicity Assessments for Substudy A

10.7.8.1.1. Efficacy Against COVID-19

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 10.7.8.5.5.1), for the purposes of the study he or she will be considered to potentially have COVID-19 illness. In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA-approved under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (ie, NAAT) to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 10.7.8.5.5.1) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.
- Confirmed severe COVID-19 (FDA definition[41]): confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an ICU;
  - Death.
- Confirmed severe COVID-19 (CDC definition[42]): confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;

- Intubation or mechanical ventilation;
- Death.

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

10.7.8.2. Safety Assessments

See Section 8.2.

10.7.8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.7.8.4. Immunogenicity Assessments

See Section 8.1.

10.7.8.5. Substudy A Procedures

10.7.8.5.1. Visit 1 – Booster Vaccination (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior participant number from Study C4591001 and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical

examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.

- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- 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 thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see Section 10.7.8.5.6), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.7.8.5.6 for further details.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.7.8.5.9).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.

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

- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

- Complete the source documents.

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

10.7.8.5.2. Visit 2 – 1-Month Telephone Contact (28 to 35 Days After Visit 1)

- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.8.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).

- Discuss contraceptive use as described in Section 5.3.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.7.8.5.9).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- 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.

10.7.8.5.3. Visit 3 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 1)

This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined the BNT162b2 booster vaccination.

- Record SAEs as described in Section 8.3.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 2 (if any).
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- 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.

10.7.8.5.4. Visit 4 – 12-Month Telephone Contact (350 to 378 Days After Visit 1)

- This visit will be conducted for all participants if the study remains blinded at the time of the visit or, if the study has been unblinded, for participants who originally received BNT162b2 or placebo recipients who declined the BNT162b2 booster vaccination.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect the participant's e-diary or assist the participant in removing 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.

10.7.8.5.5. COVID-19 Surveillance (All Substudy A Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 10.7.8.5.6) 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.

10.7.8.5.5.1. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

    - Symptoms and signs, including

        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
  - Significant acute renal, hepatic, or neurologic dysfunction
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
- Clinical diagnosis
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count
- Blood chemistry, specifically creatinine, urea, LFTs, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.6. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).

- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

10.7.8.5.7. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 1 and Visit 101: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 101 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.7.8.5.8. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analysis, as detailed in Section 10.7.9.4, or at the discretion of the study sponsor. The timing of this booster vaccination may be informed by the outcome of the interim analyses or at a time decided by the sponsor.

10.7.8.5.8.1. Visit 101 – BNT162b2 Vaccination

- Unblind the participant's study intervention assignment (if information not already available), and confirm the participant originally received only placebo at the booster vaccination visit. Secondary confirmation by another site staff member is required.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.1.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Review and consider inclusion criteria and exclusion criteria prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 3), a second sample need not be collected.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the preferably nondominant arm.
- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.7.8.5.9).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

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

10.7.8.5.8.2. Visit 102 – 1-Month Telephone Contact 2 (28 to 35 Days After Visit 101)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.7.8.5.9).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.7.8.5.5.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.5.8.3. Visit 103 – 6-Month Telephone Contact (175 to 189 Days After Visit 101)

- Contact the participant/participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since their Visit 102 (if any).
- Collect the participant's e-diary or assist the participant in removing the study application from his or her own personal device.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

10.7.8.5.9. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis. In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

10.7.9. Statistical Considerations for Substudy A

See Section 9 for master protocol statistical considerations and substudy specifics below.

10.7.9.1. Statistical Hypotheses

10.7.9.1.1. Estimands

The estimands corresponding to the primary, secondary, and exploratory objectives are described in the table in Section 10.7.3.

In the primary safety objective evaluations, missing AE start 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 efficacy objectives are based on the evaluable efficacy population (Section 10.7.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed for the all-available efficacy populations. Missing laboratory results will not be imputed.

10.7.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.7.9.1.3. Multiplicity Adjustment

No multiplicity adjustment is needed for the study as there is no statistical hypothesis.

10.7.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable efficacy	All eligible randomized participants who receive the booster vaccination as randomized and have no other important protocol deviations as determined by the clinician.
All-available efficacy (mITT)	All randomized participants who receive at least 1 dose of the study intervention.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

10.7.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.7.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

10.7.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Efficacy	**Ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose. The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time. In addition, a summary of VE over different time intervals (ie, prior to 2 months, from 2 months to 4 months, and from 4 months to 6 months after the booster dose, etc.), along with the associated 2-sided 95% CI, will be calculated using the same method. **Ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** The point estimate of VE and the associated 2-sided 95% CI, including VE at different time intervals, will be calculated using the same method as for the first primary endpoint described above.
Safety	AEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs from the booster dose to 1 month after the booster dose will be provided for each vaccine group. 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

Endpoint	Statistical Analysis Methods
	preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. Analyses methods are described in Section 9.3.1.1. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the booster dose to 6 months after the booster dose will be provided for each vaccine group.

10.7.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Efficacy	**Ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** **Ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group** For each of the above efficacy endpoints, the point estimate of VE and the associated 2-sided 95% CI for VE will be calculated using the same method as for the first primary endpoint described above.

10.7.9.3.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
Efficacy	**Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at the booster vaccination** Incidence rates (per 1000 person-years of follow-up) and 2-sided 95% CIs based on Poisson distribution for confirmed COVID-19 illness from 7 days after the booster dose will be provided for participants who received BNT162b2 at initial randomization and subsequently, respectively.

10.7.9.4. Interim Analyses

In this substudy, interim efficacy analyses were originally planned to be performed every 2 months by an unblinded statistical team to inform the timing of administration of BNT162b2 to those originally assigned to placebo. This substudy has been unblinded after the first interim analysis as informed by the outcome of the analysis; follow-up interim analyses are no longer applicable. The first interim analysis was performed after all participants reach 2 months of blinded follow-up. The final efficacy analyses to assess the primary and secondary efficacy objectives are planned to be conducted using complete blinded follow-up period data.

At each interim analysis, the following 2 estimates of VE will be obtained: (1) VE of the BNT162b2 booster group to the nonbooster group (placebo), which is the primary estimand defined for this substudy and directly estimable using the data observed in this substudy, and (2) VE of the nonbooster group (who received a primary series of 2 doses of BNT162b2 approximately 6 months prior to enrollment in this study and did not receive the BNT162b2 booster) relative to an unvaccinated population (never received a BNT162b2 primary series, not observable in this study). These estimates will be obtained using the following derivations.

Let .. $_{12}$ be the VE of the BNT162b2 booster group relative to the nonbooster group, VE_1 be the VE of the BNT162b2 booster group relative to an unvaccinated population, VE_2 be the VE of the nonbooster group relative to an unvaccinated population, IR_1 be the incidence rate of COVID-19 illness in the BNT162b2 booster group, IR_2 be the incidence rate of COVID-19 illness in the placebo booster group, and IR_0 be the nonobservable incidence rate in the unvaccinated population;

(1) VE_{12} can be estimated by observed IR_1 and IR_2 in the study as $VE_{12} = 1 - \frac{IR_1}{IR_2}$;

Since $VE_1 = 1 - \frac{IR_1}{IR_0}$, $VE_2 = 1 - \frac{IR_2}{IR_0}$,

(2) VE_2 can then be estimated by observed IR_1 and IR_2 in the study and an assumed VE_1 as

$$VE_2 = 1 - \frac{IR_2(1-VE_1)}{IR_1}.$$

Although VE_1 is also not observable from the study, it is expected that VE after the booster dose will be similar to that after the first 2 vaccine doses. Based on the results of the updated efficacy analyses from Study C4591001, the VE from 7 days to 2 months, from 2 to 4 months, and from 4 to 6 months after Dose 2 were approximately 96%, 90%, and 84%, respectively. After 6 months, a 6% drop in VE every 2 months will be assumed. These assumed values of VE_1 will be used to estimate VE_2 at the interim analyses.

If the point estimate of VE_2 (nonbooster group relative to unvaccinated population) in a 2-month interval (ie, 7 days to 2 months, 2 to 4 months, etc.) at the interim analysis is <60%, the study will be unblinded and the placebo group participants may receive BNT162b2 earlier than approximately 175 days after the vaccination at Visit 1. If VE_2 remains ≥60% at the interim analyses, all participants may remain blinded in the study and placebo recipients may not be offered BNT162b2 booster until the 12-month visit. In addition, the placebo group participants may not receive BNT162b2 as part of the study if VE_2 is ≥60% at the final analysis.

10.7.9.4.1. Analysis Timing

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

- Interim efficacy analyses after all participants reach 2 months of blinded follow-up;
- Efficacy and safety analysis at the end of the study.
- Additional analyses may be conducted if required for regulatory purposes.

10.7.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

This substudy will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

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

- Contemporaneous review of related AEs up to 1 month after the booster vaccination
- Contemporaneous review of all SAEs up to 6 months after the booster vaccination
- At the time of the planned interim analyses, and ad hoc if requested by the unblinded team, review of COVID-19 cases for an adverse imbalance of COVID-19 cases and/or severe COVID-19 cases between the vaccine and placebo groups

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

10.7.9.5. Sample Size Determination

The sample size of the study is determined to accrue sufficient COVID-19 cases for the VE assessment. Assuming a 15% nonevaluable rate, with 10,000 participants randomized in a 1:1 ratio to receive BNT162b2 booster or placebo, there will be approximately 4250 evaluable participants in each group. Table 5 presents assumptions of VE at various time intervals after the booster dose and the expected number of COVID-19 cases within each time interval with 4250 evaluable participants in each group. If the underlying incidence rate in the unvaccinated population is 0.14 per person-year follow-up, the study will accrue approximately 127 cases in 6 months. If, due to vaccination rollout and other public health measures, the incidence rate drops by 50%, approximately 63 cases are expected to be accrued in 6 months.

Table 5. Expected Number of COVID-19 Cases Under Assumed Vaccine Efficacy and Incidence Rate

Follow-Up Time Postbooster	Assumed VE			Expected Number of Cases With 4250 Evaluable Participants Per Group			
				IR_0 = 0.14/pyr		IR_0 = 0.07/pyr	
	VE_1	VE_2	VE_{12}	Boosted	Nonboosted	Boosted	Nonboosted
7 Days to 2 months	96%	72%	85.7%	3	24	2	12
2 to 4 Months	90%	66%	70.6%	10	34	5	17
4 to 6 Months	84%	60%	60.0%	16	40	8	20
7 Days to 4 months	92.8%	68.8%	76.9%	13	58	7	29
7 Days to 6 months	89.8%	65.8%	70.2%	29	98	15	49

Abbreviations: IR_0 = assumed underlying incidence rate in unvaccinated population. The observed incidence rate in placebo group of study C4591001 was 0.14 per person-year follow-up; pyr = person-years;
VE_1 = vaccine efficacy of BNT162b2 booster group relative to unvaccinated population, assumed to be similar to the vaccine efficacy after the primary vaccination series observed in Study C4591001;
VE_2 = vaccine efficacy of nonbooster group relative to unvaccinated population, assumed to have 6% drop every 2 months after the primary vaccination series and the average time after primary vaccination series at study entry is approximately 8 months for participants enrolled in this substudy;
VE_{12} = vaccine efficacy of BNT162b2 booster group to nonbooster group, calculated by $VE_{12}=1-(1-VE_1)/(1-VE_2)$.

Table 6 shows the probability to show the lower limit of the 95% CI for VE >30% for a given number of cases observed in the study under various assumed values of VE. For example, if the VE of the booster group relative to the nonbooster group is 70% over 6 months of blinded follow-up, 70 cases will provide 88.9% probability to show that the lower limit of the 95% CI for VE is >30%.

Table 6. Probability for Vaccine Efficacy Assessment

Assumed True VE	Probability to Show Lower Limit of 95% CI for VE >30% With Given Total Number of Cases				
	30 cases	50 cases	70 cases	90 cases	110 cases
60%	0.204	0.411	0.560	0.666	0.744
65%	0.306	0.579	0.743	0.842	0.902
70%	0.443	0.750	0.889	0.950	0.978
75%	0.607	0.889	0.970	0.992	0.998
80%	0.777	0.969	0.996	>0.999	>0.999

For safety outcomes, Table 7 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 0.1%, with 5000 participants in a vaccine group, there is 99% probability of observing at least 1 AE.

Table 7. Probability of Observing at Least 1 AE by Assumed True Event Rates

Sample Size (N)	Assumed True Event Rate of an AE							
	0.01%	0.05%	0.1%	0.2%	0.5%	1%	2%	5%
5000	0.39	0.92	0.99	>0.99	>0.99	>0.99	>0.99	>0.99

10.8. Appendix 8: Substudy B

10.8.1. Substudy Summary

10.8.1.1. Synopsis

See Section 1.1 for a synopsis of Substudy B.

10.8.1.2. Schema

	Visit Number	201	202	203	204	205
	Visit Description	**Vaccination 1**	**4-Day Follow-Up Visit (After Vaccination 1)**	**Vaccination 2**	**4-Day Follow-Up Visit (After Vaccination 2)**	**1-Month Follow-Up Visit (After Vaccination 2)**
Participants having received 2 or 3 prior doses of 30 µg BNT162b2, with their last dose at least 4 months (120 days) prior to randomization	Sequence 1 (n=750)	BNT162b2		Placebo		
	Sequence 2 (n=750)	Placebo		BNT162b2		
	Blood draw	10 mL	10 mL	10 mL	10 mL	10 mL

10.8.1.3. Schedule of Activities for Substudy B

Visit Number	201	202	203	204	205
Visit Description	**Vaccination 1**	**4-Day Follow-Up Visit (After Vaccination 1)**	**Vaccination 2**	**4-Day Follow-Up Visit (After Vaccination 2)**	**1-Month Follow-Up Visit (After Vaccination 2)**
Visit Window	**Day 1[a]**	**2-5 Days After Visit 201**	**28-35 Days After Visit 201**	**2-5 Days After Visit 203**	**28-35 Days After Visit 203**
Confirm that the participant has received 2 or 3 prior doses of BNT162b2, with their last dose at least 4 months (120 days) prior to randomization; secondary confirmation by another site staff member is required	X				
Obtain informed consent/assent[b]	X				
Obtain the participant's prior study and participant number (if applicable)	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment[c]	X				
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X		X
Measure height and weight	X				
Measure temperature (body)	X		X		
Perform urine pregnancy test (if appropriate)	X		X		
Confirm use of contraceptives (if appropriate)	X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X		X		
Review temporary delay criteria	X		X		
Collect blood sample	~10 mL	~10 mL	~10 mL	~10 mL	~10 mL
Obtain randomization number	X				
Obtain study intervention allocation	X		X		
Administer study intervention	X		X		
Assess acute reactions for at least 30 minutes after study intervention administration	X		X		

Visit Number	201	202	203	204	205
Visit Description	**Vaccination 1**	**4-Day Follow-Up Visit (After Vaccination 1)**	**Vaccination 2**	**4-Day Follow-Up Visit (After Vaccination 2)**	**1-Month Follow-Up Visit (After Vaccination 2)**
Visit Window	**Day 1[a]**	**2-5 Days After Visit 201**	**28-35 Days After Visit 201**	**2-5 Days After Visit 203**	**28-35 Days After Visit 203**
Explain/review participant communication methods (including for reactogenicity e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X		X		
Provide/ensure participant has a thermometer and measuring device	X		X		
Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration)	X →	X →	X →	X →	X
Review ongoing reactogenicity e-diary symptoms with participant and obtain and record stop dates		X	X	X	X
Collect the e-diary device or assist the participant to delete the application					X
Collect AEs and SAEs as appropriate	X	X	X	X	X[d]
Contact the participant by telephone					

Abbreviation: HIV = human immunodeficiency virus.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. For participants <18 years of age (at the time of consent), the parent(s)/legal guardian will provide signed informed consent. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).
c. Including, if indicated, a physical examination.
d. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.8.2. Introduction

10.8.2.1. Study Rationale

Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men after the second dose of the vaccine, and within 14 days after vaccination. These events are generally mild, and individuals tend to recover within a short time following standard treatment and rest. However, the incidence of subclinical myocarditis and pericarditis prior to the presentation of overt clinical signs and symptoms is unknown. Therefore, this protocol's Substudy B will assess the safety and tolerability of a single dose of BNT162b2 as compared to placebo control, through the potential analysis of serum troponin levels, in participants ≥12 and ≤30 years of age who have received 2 or 3 prior doses of BNT162b2 (30-µg doses), with their last dose at least 4 months (120 days) prior to randomization.

10.8.2.2. Background

See Section 2.2 for the study background.

10.8.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy B beyond those detailed for the master study (see Section 2.3).

10.8.2.3.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy B may be:

- Receipt of a booster (third) dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Contributing to research to help others in a time of global pandemic.

10.8.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the frequency of elevated troponin I levels before and after a booster dose of BNT162b2 or placebo	In participants receiving 1 dose of study intervention, the percentage of participants with elevated troponin I levels before and at subsequent time points after a booster dose of BNT162b2 or placebo	• Troponin I level
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each vaccination • Systemic events for up to 7 days following each vaccination • AEs within 1 month after each vaccination • SAEs within 1 month after each vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

10.8.4. Study Design

10.8.4.1. Overall Design

This is a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥12 years of age to ≤30 years of age who have received 2 or 3 prior doses of BNT162b2 (30-µg doses), with their last dose at least 4 months (120 days) prior to randomization, will be enrolled. Participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at Visit 201 and the alternative at Visit 203, four weeks later. Randomization will be stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Approximately 1500 participants will be randomized in the study. A blood sample will be collected to obtain a serum sample for troponin testing before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration.

10.8.4.2. Scientific Rationale for Substudy B Design

See Section 10.8.2.1.

10.8.4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

10.8.4.3. Justification for Dose

See Section 4.3 for a justification of the BNT162b2 dose used in Substudy B.

10.8.4.4. End of Study Definition

See Section 4.4.

10.8.5. Study Population

Details of the master eligibility criteria are shown in Section 5. Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy B–specific inclusion and exclusion criteria.

10.8.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants 12 to 30 years of age, inclusive, who have received 2 or 3 prior doses of 30 µg BNT162b2 (with the first 2 doses 19 to 60 days apart), with the last dose being at least 4 months (120 days) before Visit 1 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

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

Type of Participant and Disease Characteristics:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.15.

Informed Consent:

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

   The investigator, or a person designated by the investigator, will obtain written/electronically signed informed consent (and assent) from each study participant's legal guardian (as defined in Appendix 1), and the participant's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

10.8.5.2. Exclusion Criteria

Participants are excluded from Substudy B 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. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

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

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

6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study.

Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

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

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

12. Prior receipt of more than 3 doses of BNT162b2 30 µg.

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

10.8.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy B as detailed in Section 5.3 and Section 10.4.

10.8.5.4. Screen Failures

See Section 5.4.

10.8.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.8.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg
- Normal saline (0.9% sodium chloride solution for injection)

10.8.6.1. Study Intervention(s) Administered

See Section 6.1 for details of BNT162b2.

Additional Intervention Name	Saline Placebo
Type	Placebo
Dose Formulation	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	N/A
Dosage Level(s)	N/A
Route of Administration	Intramuscular injection
Use	Placebo
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	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

10.8.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 201 (Vaccination 1) and Visit 203 (Vaccination 2) in accordance with the substudy's SoA (Section 10.8.1.3).

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

10.8.6.1.2. Preparation and Dispensing

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

10.8.6.2. Measures to Minimize Bias: Randomization and Blinding

10.8.6.2.1. Blinding of Site Personnel

In this observer-blinded substudy, 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 there are differences in physical appearance of the study interventions, the study intervention will be administered in a manner that prevents the study participants from identifying the study intervention sequence based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the

unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.8.6.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 10.8.9.4.1). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

The participant may be unblinded at Visit 205, 1 month after receiving their second study vaccination, to confirm the date of BNT162b2 receipt. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.8.6.2.3. 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.

10.8.6.3. Study Intervention Compliance

See Section 6.4.

10.8.6.4. Dose Modification

See Section 6.5.

10.8.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.8.6.6. Treatment of Overdose

See Section 6.7.

10.8.6.7. Concomitant Therapy

See Section 6.8.

10.8.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.8.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 50 mL.

For all participants, 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.

10.8.8.1. Safety Assessments

See Section 8.2.

10.8.8.2. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.8.8.3. Substudy B Procedures

10.8.8.3.1. Visit 201 – Vaccination (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Confirm that the participant has received 2 or 3 prior doses of BNT162b2 (30-µg doses) with their last dose at least 4 months (120 days) prior to randomization. Secondary confirmation by another site staff member is required.
- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample (approximately 10 mL) for troponin levels.

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.

- 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.

- Explain the e-diary technologies available for this study (see Section 8.2.4), and assist the participant or his/her parent(s)/legal guardian(s), as appropriate, in downloading the study application onto his or her own device or issue a provisioned device if required.

- Provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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.

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

- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.8.8.3.6).

- Ask the participant or his/her parent(s)/legal guardian(s), as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian to bring the reactogenicity 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.

10.8.8.3.2. Visit 202 – 4-Day Follow-Up Visit (After Vaccination 1) (2-5 Days After Visit 201)

- Record AEs as described in Section 8.3.
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 10 mL) for troponin levels.
- Discuss contraceptive use as described in Section 5.3.
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.8.8.3.6).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit. Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.8.8.3.3. Visit 203 – Vaccination 2 (28 to 35 Days After Visit 201)

- Record AEs as described in Section 8.3.
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 201 (if any).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

  Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please 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 10 mL) for troponin levels.
- Unblinded site staff will obtain the participant's study intervention allocation using the IRT system.
- Unblinded site staff will 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 that the participant or his/her parent(s)/legal guardian has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure that the participant or his/her parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Discuss contraceptive use as described in Section 5.3.

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.8.8.3.6).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

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

- Remind the participant or his/her parent(s)/legal guardian to bring the reactogenicity 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.

10.8.8.3.4. Visit 204 – 4-Day Follow-Up Visit (After Vaccination 2) (2 to 5 Days After Visit 203)

- Record AEs as described in Section 8.3.

- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).

- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.

- Record nonstudy vaccinations as described in Section 6.8.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- Collect a blood sample (approximately 10 mL) for troponin levels.

- Discuss contraceptive use as described in Section 5.3.
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.8.8.3.6).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.8.8.3.5. Visit 205 – 1-Month Follow-Up Visit (After Vaccination 2) (28-35 Days After Visit 203)

- Record AEs as described in Section 8.3.
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 203 (if any).Collect a blood sample (approximately 10 mL) for troponin levels.
- Collect the participant's e-diary or assist the participant or his/her parent(s)/legal guardian in removing 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.

- The participant may be unblinded at Visit 205, 1 month after receiving their second study vaccination, to confirm the date of BNT162b2 receipt. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.8.8.3.6. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level (Results from the blood samples collected during the study will be provided to the participant's study physician; however, this will take some time, so the participant should be cautioned not to rely on these results for medical treatment.)

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

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

If a Grade 3 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 a suspected Grade 4 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

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

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.

- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).

- The PI or authorized designee determined it was not needed.

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

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

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

- Measure body temperature (°F/°C).

- Measure minimum and maximum diameters of redness (if present).

- Measure minimum and maximum diameters of swelling (if present).

- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.4.2.

- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.4.3.

- 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.

10.8.9. Statistical Considerations for Substudy B

See Section 9 for master protocol statistical considerations and substudy specifics below.

10.8.9.1. Statistical Hypotheses

10.8.9.1.1. Estimands

The estimands corresponding to the primary objectives are described in the table in Section 10.8.3.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.8.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.8.9.1.3. Multiplicity Adjustment

No multiplicity adjustment is needed for the study as there is no statistical hypothesis.

10.8.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Safety	All participants who receive at least 1 dose of the study intervention.

10.8.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary endpoints.

10.8.9.3.1. General Considerations

All safety data will be analyzed separately for each age group (12-17, 18-24, and 25-30 years of age) and for all age groups combined.

Refer to Section 9.3.1 for general considerations of statistical analyses.

10.8.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Safety	Counts and percentages of participants with elevated troponin I levels before and 4 days and 1 month after administration of BNT162b2 or placebo will be provided for Sequence 1 and Sequence 2 combined. The associated Clopper-Pearson 95% CIs will also be provided (Section 9.3.1.1). The difference in percentages of participants with elevated troponin I levels between BNT162b2 and placebo will be provided at each time point after vaccination (4 days after BNT162b2 minus 4 days after placebo, or 1 month after BNT162b2 minus 1 month after placebo) combining Sequence 1 and Sequence 2. This analysis will be limited to participants with troponin I level measurements at both time points. The

Endpoint	Statistical Analysis Methods
	2-sided 95% CI for the difference in percentages will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)[43] for comparing matched proportions. The difference in percentages of participants with elevated troponin I levels between before and after each vaccination (ie, 4 days after BNT162b2 minus before BNT162b2, 4 days after placebo minus before placebo) and associated 95% CI will be summarized in a similar way. Additional assessment based on the crossover design feature may be performed and details will be described in the SAP. In addition, percentages of participants with elevated troponin I levels before and at subsequent time points after each vaccination will be summarized for Sequence 1 and Sequence 2 separately. Descriptive statistics will be provided for each reactogenicity endpoint after each vaccination for Sequence 1 and Sequence 2 separately. Local reactions and systemic events from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs (Section 9.3.1.1). Local reactions and systemic events within 7 days after BNT162b2 or placebo administration will also be summarized in a similar way for Sequence 1 and Sequence 2 combined. AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs and SAEs within 1 month after each vaccination will be provided for Sequence 1 and Sequence 2 separately (Section 9.3.1.1). AEs/SAEs will also be summarized within 1 month after BNT162b2 or placebo administration in a similar way for Sequence 1 and Sequence 2 combined.

10.8.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Not applicable.

10.8.9.3.4. Exploratory Endpoint(s)

Not applicable.

10.8.9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Only 1 analysis will be performed at the completion of the study.

10.8.9.4.1. Data Monitoring Committee or Other Independent Oversight Committee

This substudy will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

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

10.8.9.5. Sample Size Determination

The study size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes based on anticipated enrollment in each age group and overall. For example, if the true AE rate is 0.10%, with 750 participants in each randomized sequence, there is 53% probability of observing at least 1 AE.

Table 8. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Samples Sizes

Sample Size (N)	Assumed True Event Rate of an AE						
	0.01%	**0.02%**	**0.05%**	**0.10%**	**0.50%**	**1.00%**	**2.00%**
250	0.02	0.05	0.12	0.22	0.71	0.92	>0.99
500	0.05	0.10	0.22	0.39	0.92	>0.99	>0.99
750	0.07	0.14	0.31	0.53	0.98	>0.99	>0.99
1500	0.14	0.26	0.53	0.78	>0.99	>0.99	>0.99

Note: A total of 250 and 500 participants are to be enrolled in each age group within each randomized sequence and overall. A total of 750 and 1500 participants are to be enrolled for all age groups within each randomized sequence and overall.

10.9. Appendix 9: Substudy C

10.9.1. Substudy Summary

10.9.1.1. Synopsis

See Section 1.1 for a synopsis of Substudy C.

10.9.1.2. Schema

	Visit Number	301	302	303	304	305
	Visit Description	**Booster (Third) Dose of BNT162b2**	**7 Days After Booster Vaccination**	**1 Month After Booster Vaccination**	**6 Months After Booster Vaccination**	**12 Months After Booster Vaccination**
Participants having received 2 prior doses of 30 µg BNT162b2 at least 5 months (150 days) prior to randomization		BNT162 10-µg OR 30-µg dose				
	Blood draw for immunogenicity[a]	10 mL/ 20 mL	10 mL/ 20 mL	10 mL/ 20 mL	10 mL/ 20 mL	10 mL/ 20 mL

a. Approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants in the 12- to 17-year age stratum.

10.9.1.3. Schedule of Activities for Substudy C

Visit Number	301	302	303	304	305
Visit Description	**Booster (Third) Dose of BNT162b2**	**7 Days After Booster Vaccination**	**1 Month After Booster Vaccination**	**6 Months After Booster Vaccination**	**12 Months After Booster Vaccination**
Visit Window	**Day 1[a]**	**6-8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**175-189 Days After Visit 301**	**350-378 Days After Visit 301**
Confirm the participant has only received 2 doses of BNT162 at least 5 months (150 days) prior to randomization.	X				
Obtain informed consent/assent	X				
Obtain the participant's prior study and participant number (if applicable)	X				
Assign participant number	X				
Obtain demography and medical history data	X				
Perform clinical assessment[b]	X				
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X
Measure height and weight	X				
Measure temperature (body)	X				
Perform urine pregnancy test (if appropriate)	X				
Confirm use of contraceptives (if appropriate)	X	X	X		
Collect nonstudy vaccine information	X	X	X		
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity[c]	~20 mL/~10 mL	~20 mL/~10 mL	~20 mL/~10 mL	~20 mL/~10 mL	20 mL/~10 mL
Obtain randomization number	X				
Obtain study intervention allocation	X				
Administer study intervention	X				
Assess acute reactions for at least 30 minutes after study intervention administration	X				
Explain/review participant communication methods (including for reactogenicity e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X				
Provide/ensure participant has a thermometer and measuring device	X				

Visit Number	301	302	303	304	305
Visit Description	**Booster (Third) Dose of BNT162b2**	**7 Days After Booster Vaccination**	**1 Month After Booster Vaccination**	**6 Months After Booster Vaccination**	**12 Months After Booster Vaccination**
Visit Window	**Day 1[a]**	**6-8 Days After Visit 301**	**28 to 35 Days After Visit 301**	**175-189 Days After Visit 301**	**350-378 Days After Visit 301**
Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following study intervention administration)	X →	X →			
Review ongoing reactogenicity e-diary symptoms with participant and obtain stop dates		X	X		
Request the participant return the e-diary or assist the participant to delete the application			X		
Collect AEs and SAEs as appropriate	X	X	X	X[d]	X[d]

Abbreviation: HIV = human immunodeficiency virus.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. Including, if indicated, a physical examination.
c. 20 mL is to be collected from participants ≥18 years of age; 10 mL is to be collected from participants 12 to 17 years of age.
d. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.9.2. Introduction

10.9.2.1. Study Rationale

Substudy C will assess the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at doses of 10 µg or 30 µg in participants who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months (150 days) prior to randomization. The primary immunogenicity objective of the study is to demonstrate that the immune response induced by a booster (third) dose of BNT162b2 at a 10-µg dose is noninferior to the immune response elicited 1 month after the second dose of BNT162b2 at 30 µg (ie, having completed a 2-dose primary series of BNT162b2 [30-µg doses]).

If this objective is successfully met, a lower dose level would allow for greater vaccine accessibility and equity – with more doses being available globally. A more favorable reactogenicity profile may also be demonstrated. Additionally, the results from 306 participants 18 to 55 years of age from the C4591001 study who received a third (booster) dose of 30 µg BNT162b2 a median of 6.8 months after their second dose demonstrated a strong immune response with robust neutralizing antibody titers against the reference strain.[20] Immunogenicity of the primary series in participants 12 to 15 of age was shown to be greater than in participants 16 to 25 years of age.[21] Therefore, the assessment of a 10-µg booster dose in individuals ≥12 years of age who have received the authorized 30-µg 2-dose primary series warrants further investigation. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results. This study contains assessments that could be considered standard for a vaccine noninferiority study. Blood samples taken for immunogenicity will establish the level of immune response elicited by each dose level to provide the necessary data to meet the primary endpoint of the study. Immunogenicity will be assessed by SARS-CoV-2 neutralizing titers.

See Section 2.2 for the study background.

10.9.2.2. Benefit/Risk Assessment

No additional risks are identified for Substudy C beyond those detailed for the master study (see Section 2.3).

10.9.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy C may be:

- Receipt of a booster dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.
- Receipt of a potentially efficacious booster dose with the potential of reduced reactogenicity.
- Contributing to research to help others in a time of global pandemic.

10.9.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
• To evaluate the safety of a booster dose of BNT162b2 when administered at both 10-µg and 30-µg doses	In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants reporting: • Local reactions for up to 7 days following the booster dose • Systemic events for up to 7 days following the booster dose • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
For each of the 2 age groups (12 through 17 years of age and ≥56 years of age): To demonstrate that the immune responses induced by a booster (third) dose of BNT162b2 at 30 µg at 1 month after the third dose is noninferior to the immune responses induced by the second dose at 1 month after the second dose in age-matched participants (control group) randomly selected from the C4591001 study without evidence of SARS-CoV-2 infection (up to 1 month after receipt of the third dose for participants who received the third dose, and up to 1 month after receipt of the second dose for participants in the control group)	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of the third dose for participants who received the third dose, and up to 1 month after receipt of the second dose for participants in the control group) of past SARS-CoV-2 infection: • GMR, estimated by the ratio of the GMTs of SARS-CoV-2 neutralizing titers at 1 month after the third dose in participants who received a booster (third) dose of BNT162b2 at 30 µg to those at 1 month after the second dose in age-matched participants randomly selected from the C4591001 study • The difference in the percentage of participants with seroresponse at 1 month after the third dose in participants who received a booster (third) dose of BNT162b2 at 30 µg and at 1 month after the second dose in age-matched participants randomly selected from the C4591001 study	• SARS-CoV-2 neutralizing titers
For each of the 4 age groups (12 through 17 years of age, 18 through 30 years of age, 31 through 55 years of age, and ≥56 years of age): To demonstrate that the immune responses induced by a booster (third) dose of BNT162b2 at 10 µg at 1 month after the third dose is noninferior to the immune responses induced by the second dose at 1 month after the second dose in age-matched participants (control group) randomly selected from the C4591001 study without evidence of SARS-CoV-2 infection (up to 1 month after receipt of the third dose for participants who received the third	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of the third dose for participants who received the third dose, and up to 1 month after receipt of the second dose for participants in the control group) of past SARS-CoV-2 infection in each age group: • GMR, estimated by the ratio of the GMTs of SARS-CoV-2 neutralizing titers at 1 month after the third dose in participants who received a booster (third) dose of BNT162b2 at 10 µg to those at 1 month after the second dose in age-matched	• SARS-CoV-2 neutralizing titers

Objectives	Estimands	Endpoints
dose, and up to 1 month after receipt of the second dose for participants in the control group)	participants randomly selected from the C4591001 study • The difference in the percentage of participants with seroresponse at 1 month after the third dose in participants who received a booster (third) dose of BNT162b2 at 10 µg and at 1 month after the second dose in age-matched participants randomly selected from the C4591001 study	
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
To describe the immune responses induced by a booster (third) dose of BNT162b2 at 10 µg and 30 µg	In evaluable participants with no serological or virological evidence of past SARS-CoV-2 infection from each vaccine and age group: At baseline (before the third dose) and 7 days, 1 month, 6 months, and 12 months after the third dose: • GMTs at each time point • GMFRs from baseline (before the third dose) to each subsequent time point after the third dose	• SARS-CoV-2 neutralizing titers
Exploratory Immunogenicity	**Exploratory Immunogenicity**	**Exploratory Immunogenicity**
To describe the immune response to VOCs		• SARS-CoV-2 neutralizing titers for VOCs

Note: Seroresponse is defined as achieving ≥4 × LLOQ.

10.9.4. Study Design

10.9.4.1. Overall Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg or 30 µg. Participants ≥12 years of age who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months (150 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive BNT162b2 at either a 10-µg or 30-µg dose level at Visit 301. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results at 7 days after the third dose. A DMC will review safety (e-diary and AE) and immunogenicity data in the first approximately 100 participants with available immunogenicity in each age group (~50 participants in each dose level) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of the next age group will occur independently. Please refer to Table 9 for details.

Table 9. Total Number of Participants by Age Group and Dose Level

Age Group	Dose Level	Total Number of Participants per Dose Level	Total Number of Participants per Age Group
12-17 Years	10 µg, 30 µg	300	600
18-30 Years	10 µg, 30 µg	300	600
31-55 Years	10 µg, 30 µg	300	600
≥56 Years	10 µg, 30 µg	300	600

Serum blood samples will be collected for immunogenicity at baseline, 7 days after the booster (third) dose, 1 month after the third dose, 6 months after the third dose, and 12 months after the third dose. Up to approximately 2400 participants will be randomized in the study.

10.9.4.1.1. Scientific Rationale for Substudy C Design

See Section 1.1.

10.9.4.1.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

10.9.4.2. Justification for Dose

See Section 4.3 for a justification of the 30-µg BNT162b2 dose used in Substudy C.

If a booster (third) dose of BNT162b2 at 10 µg induces an immune response that is noninferior to the immune responses elicited 1 month after the second dose of BNT162b2 at 30 µg (ie, following completion of a 2-dose primary series of BNT162b2 [30-µg doses]), this finding could have significant implications on vaccine accessibility and equity globally, as it would allow for the availability of more doses.

10.9.4.3. End of Study Definition

See Section 4.4.

10.9.5. Study Population

Details of the master and Substudy C eligibility criteria are shown in Section 5. Participants must meet all of the general inclusion and exclusion criteria as specified for both the master protocol and Substudy C–specific inclusion and exclusion criteria.

10.9.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥12 years of age, inclusive, who have received 2 prior doses of 30 µg BNT162b2 19 to 60 days apart, with the second dose being at least 150 days before Visit 301 (Day 1)

   Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

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

   Type of Participant and Disease Characteristics:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.15.

Informed Consent:

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

   The investigator, or a person designated by the investigator, will obtain written/electronically signed informed consent (and assent) from each study participant's legal guardian (as defined in Appendix 1, and the participant's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

10.9.5.2. Exclusion Criteria

Participants are excluded from Substudy C 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. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

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

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

6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

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

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

12. Prior receipt of more than 2 doses of BNT162b2 30 µg.

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

10.9.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy C as detailed in Section 5.3 and Section 10.4.

10.9.5.4. Screen Failures

See Section 5.4.

10.9.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.9.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

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

10.9.6.1. Study Intervention(s) Administered

See Section 6.1 for details of BNT162b2.

10.9.6.1.1. Administration

Participants will receive 1 dose of study intervention at Visit 301 (booster [third] dose of BNT162b2) in accordance with the substudy's SoA (Section 10.9.1.3).

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

10.9.6.1.2. Preparation and Dispensing

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

10.9.6.2. Measures to Minimize Bias: Randomization and Blinding

10.9.6.2.1. Blinding of Site Personnel

In this observer-blinded substudy, 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.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.9.6.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 10.9.9.4.2). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

The participant may be unblinded to confirm the dose of BNT162b2 received 3 months after receiving their study vaccination. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.9.6.2.3. 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.

10.9.6.3. Study Intervention Compliance

See Section 6.4.

10.9.6.4. Dose Modification

See Section 6.5.

10.9.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.9.6.6. Treatment of Overdose

See Section 6.7.

10.9.6.7. Concomitant Therapy

See Section 6.8.

10.9.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.9.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 100 mL. For participants 12 through 17 years of age, approximately 50 mL of blood will be collected.

For all participants, 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.

10.9.8.1. Efficacy and/or Immunogenicity Assessments for Substudy C

10.9.8.1.1. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The test to be performed will be the SARS-CoV-2 neutralizing assay. Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

10.9.8.2. Safety Assessments

See Section 8.2.

10.9.8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.9.8.4. Substudy C Procedures

10.9.8.4.1. Visit 301 – Booster (Third) Dose of BNT162b2 (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Confirm the participant has only received 2 doses of BNT162b2 at least 5 months (150 days) prior to randomization. Secondary confirmation by another site staff member is required.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants in the 12- to 17-year age stratum).
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- 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.

- Explain the e-diary technologies available for this study (see Section 8.2.4), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto his or her own device or issue a provisioned device if required.

- Provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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.

- 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.

- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).

- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.5).

- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

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

- Complete the source documents.

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

10.9.8.4.2. Visit 302 – 7 Days After Booster Vaccination (6-8 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Collect a blood sample for immunogenicity (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants in the 12- to 17-year age stratum).
- Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following each study intervention administration).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Discuss contraceptive use as described in Section 5.3.
- Ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.5).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- 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.

10.9.8.4.3. Visit 303 – 1 Month After Booster Vaccination (28 to 35 Days After Visit 301)

- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 301 (if any).
- Record AEs as described in Section 8.3.

- Collect a blood sample for immunogenicity (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants in the 12- to 17-year age stratum).
- Review ongoing reactogenicity e-diary symptoms with the participant and obtain and record stop dates.
- Collect the participant's reactogenicity e-diary or assist the participant or his/her parent(s)/legal guardian to remove the study application from his or her own personal device.
- Discuss contraceptive use as described in Section 5.3.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

10.9.8.4.4. Visit 304 – 6 Months After Booster Vaccination (175 to 189 Days After Visit 301)

- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 303 (if any).
- Collect a blood sample for immunogenicity (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants in the 12- to 17-year age stratum).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.9.8.4.5. Visit 305 – 12 Months After Booster Vaccination (350 to 378 Days After Visit 301)

- Record AEs as described in Section 8.3.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 304 (if any).
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- Collect a blood sample for immunogenicity (approximately 20 mL for participants ≥18 years of age and approximately 10 mL for participants in the 12- to 17-year age stratum).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.9.8.5. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

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

If a Grade 3 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

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

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

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

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined that 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 8.2.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.4.3.

- 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.

10.9.9. Statistical Considerations for Substudy C

See Section 9 for master protocol statistical considerations and substudy specifics below.

10.9.9.1. Statistical Hypotheses

10.9.9.1.1. Estimands

The estimands corresponding to the primary and secondary objectives are described in the table in Section 10.9.3.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.9.9.1.2. Statistical Hypotheses

The primary immunogenicity objectives are to assess the noninferiority of the immune response induced by a booster (third) dose of BNT162b2 at 10 µg (or 30 µg) 1 month after the third dose relative to the immune response elicited by the first 2 doses at 1 month after the second dose in the C4591001 study.

There are 2 null hypotheses for each dose level in the 12- to 17-year age group and ≥56-year age group and for the 10-µg dose level in the 18- to 30-year age group and 31-to 55-year age group:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 neutralizing titers measured at 1 month after the third dose in participants who received the third dose;

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 neutralizing titers measured at 1 month after the second dose in age-matched participants (control group) randomly selected from the C4591001 study.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.1 \text{ Vs } p_1 - p_2 > -0.1$$

where -10% is the margin for noninferiority for seroresponse and

  - p_1 is the percentage of participants with seroresponse at 1 month after the third dose in participants who received the third dose;
  - p_2 is the percentage of participants with seroresponse at 1 month after the second dose in age-matched participants (control group) randomly selected from the C4591001 study.

For each dose level in each age group, noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8; noninferiority based on seroresponse rate difference will be declared if the lower limit of the CI for the difference in percentages of participants with seroresponse is >-10%.

Seroresponse is defined as achieving ≥4 × LLOQ.

10.9.9.1.3. Multiplicity Adjustment

For the immunogenicity objectives of noninferiority in each of the 4 age groups (12-17 years, 18-30 years, 31-55 years, and ≥56 years) and each of the booster dose levels, the hypothesis testing for each age group will be carried out separately. Each noninferiority analysis corresponds to a separate analysis of the respective age group, with a separate objective. The age groups are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied in the immunogenicity assessments for the 4 age groups.

Within each age group, noninferiority for each booster dose level (12-17 years and ≥56 years only) will be evaluated sequentially for the 30-µg booster dose level first, followed by the 10-µg booster dose level. Within each booster dose level, noninferiority based on GMR and seroresponse difference will be assessed sequentially in the order as specified. Noninferiority for the 10-µg dose level will be assessed only if noninferiority of the 30-µg booster dose level is established for both GMR and seroresponse difference. Therefore, the overall type I error is fully controlled.

10.9.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.

Population	Description
Evaluable immunogenicity	All eligible randomized participants who receive the study vaccine to which they are randomized, have a valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive at least 1 dose of the study intervention.

10.9.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.9.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

In this substudy, all safety and immunogenicity data will be analyzed separately for each age group.

10.9.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group in each age group. Local reactions and systemic events from Day 1 through Day 7 after the third dose (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after the third dose will be provided for each vaccine group within each age group. A 3-tier approach will be used to summarize AEs in this study. 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

Endpoint	Statistical Analysis Methods
	MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group in each age group will be provided separately.
Immunogenicity	**GMRs of SARS-CoV-2 neutralizing titers at 1 month after the third dose in participants who received a booster (third) dose to those at 1 month after the second dose of BNT162b2 in age-matched participants (control group) randomly selected from the C4591001 study for each dose level in the 12- to 17-year age group and ≥56-year age group and for the 10-µg dose level in the 18- to 30-year age group and the 31- to 55-year age group.** **The differences in percentages of participants with seroresponse at 1 month after the booster (third) dose in participants who received a booster (third) dose and at 1 month after the second dose of BNT162b2 in age-matched participants (control group) randomly selected from the C4591001 study for each dose level in the 12- to 17-year age group and ≥56-year age group and for the 10-µg dose level in the 18- to 30-year age group and the 31- to 55-year age group.** • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers at 1 month after the third dose in participants who received a booster (third) dose to those at 1 month after the second dose in age-matched participants (control group) randomly selected from the C4591001 study, will be provided along with associated 2-sided 95% CIs (see Section 9.3.1.2.3). Only participants with no serological or virological evidence (up to 1 month after receipt of the third dose for participants enrolled in this study, or up to 1 month after the second dose for the age-matched control group participants) of past SARS-CoV-2 infection will be included in the analysis. • The percentages of participants with seroresponse at the specified time point for each group and the difference in percentages will be provided. The difference in percentages of participants with

Endpoint	Statistical Analysis Methods
	seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (see Section 9.3.1.1). • Only participants with no serological or virological evidence (up to 1 month after receipt of the third dose for participants enrolled in this study, or up to 1 month after the second dose for the age-matched control group participants) of past SARS-CoV-2 infection will be included in the analysis. • Noninferiority based on GMR will be established if the lower bound of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -10%.

10.9.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMTs and GMFRs of SARS-CoV-2 neutralizing titers** • GMTs at each time point and GMFRs of SARS-CoV-2 neutralizing titers from baseline (before the third dose) to each subsequent time point after vaccination will be provided in participants with no serological or virological evidence of past SARS-CoV-2 infection using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. Participants' data will be excluded from the time point that the participant is determined as a COVID-19 case or has a positive N-binding antibody result. GMFRs will be limited to participants with nonmissing values prior to the third dose and at the postvaccination time point.

10.9.9.3.4. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMTs of SARS-CoV-2 neutralizing titers for VOCs** • GMTs of VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs and GMRs of VOC-neutralizing titers to reference-strain–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.

10.9.9.4. Interim Analyses

An administrative interim analysis is planned for each of the following age groups: 12 through 17 years, 18 through 30 years, and 31 through 55 years, when 7-day post–booster dose immunogenicity data are available from approximately the first 100 participants (~50 participants in each booster dose–level group). The purpose of the administrative interim analysis is to inform initiation of enrollment for the next age group. The analysis will be performed by an unblinded DMC reporting team. Only group-level unblinded results will be shared with limited sponsor personnel.

Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

10.9.9.4.1. Analysis Timing

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

- Safety data through 1 month after the third dose in each dose level group and age group.
- Immunogenicity data through 1 month after the third dose for participants enrolled in this study and through 1 month after Dose 2 for the comparator group from the C4591001 study in each age group (noninferiority comparison of SARS-CoV-2 neutralizing titers compared to the comparator group from the C4591001 study).
- Complete safety and immunogenicity analysis approximately 6 months after the third dose in each dose group and age group.
- Complete safety and immunogenicity analysis approximately 12 months after the third dose in each dose group and age group.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses conducted while the study is ongoing will be performed by an unblinded team.

10.9.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize a DMC that will be used to review safety data (e-diary and AE) and immunogenicity in the first approximately 100 participants with available immunogenicity data in each age group (~50 participants in each dose level of BNT162b2) to guide age escalation 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of each age group will occur independently.

The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

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

10.9.9.5. Sample Size Determination

The sample size of the study is based on consideration of acceptable safety database. A random sample of approximately 175 participants from each age group and booster dose–level group will be selected from all participants enrolled in the study for the noninferiority evaluation for the primary immunogenicity endpoint, SARS-CoV-2 neutralizing titers 1 month after a booster (third) dose to 1 month after the second dose in the C4591001 study, using a 1.5-fold noninferiority margin for GMR and -10% for percentage of seroresponse in each booster dose level in each age group. The same number of age-matched participants for each age group will be selected from the C4591001 study as a control group for the immunogenicity evaluation.

Assuming a 25% nonevaluable rate, approximately 130 evaluable participants in each booster dose group in each age group will contribute to the immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations.

In each age group, for comparisons based on GMR, common assay standard deviations at 1 month after a booster dose or 1 month after Dose 2 in the C4591001 study in log scale is assumed to be 0.93 based on data observed in the C4591001 study. A GMR of 1 is assumed for each comparison. For comparisons based on seroresponse, a 95% response rate is assumed for each comparative group at the comparative time point. With 130 evaluable participants and the stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has 93.3% power to demonstrate noninferiority based on GMR for the objectives in each booster dose level using a 1.5-fold margin and 90.4% power to declare noninferiority based on seroresponse rate using a 10% margin.

For safety outcomes, Table 10 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, with 300 participants in a vaccine group, there is 95% probability of observing at least 1 AE.

Table 10. Probability of Observing at 1 Least AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=50	N=100	N=300	N=600	N=2400
0.01%	0	0.01	0.03	0.06	0.26
0.02%	0.01	0.02	0.06	0.11	0.45
0.04%	0.02	0.04	0.11	0.21	0.7
0.06%	0.03	0.06	0.16	0.3	0.83
0.08%	0.04	0.08	0.21	0.38	0.91
0.10%	0.05	0.1	0.26	0.45	0.95
0.15%	0.07	0.14	0.36	0.59	0.99
0.20%	0.1	0.18	0.45	0.7	>0.99
0.25%	0.12	0.22	0.53	0.78	>0.99
0.30%	0.14	0.26	0.59	0.84	>0.99
0.50%	0.22	0.39	0.78	0.95	>0.99
1.00%	0.39	0.63	0.95	>0.99	>0.99
2.00%	0.64	0.87	>0.99	>0.99	>0.99
3.00%	0.78	0.95	>0.99	>0.99	>0.99
5.00%	0.92	0.99	>0.99	>0.99	>0.99
10.0%	0.99	>0.99	>0.99	>0.99	>0.99

10.10. Appendix 10: Substudy D

10.10.1. Substudy Summary

10.10.1.1. Synopsis

See Section 1.1 for a synopsis of Substudy D.

10.10.1.2. Schema

10.10.1.2.1. Participants in Cohort 1

Cohort	Visit Number	401	402	403	404	405	406
	Visit Description	**SSD Vaccination 1**	**1-Month Follow-Up Visit and SSD 2nd Vaccination**	**1-Month Follow-Up Visit after SSD 2nd Vaccination[a]**	**3-Month Follow-Up Visit After Last SSD Vaccination**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**
Cohort 1: Participants 18-55 years of age having received 2 doses of BNT162b2 before enrollment (3-8 months after last dose)	Group 1: (N=205)	BNT162b2 OMI 30-µg dose					
	Group 2: (N=205)	BNT162b2 OMI 30-µg dose	BNT162b2 OMI 30-µg dose				
	Group 2b: (N=205)	BNT162b2 30-µg dose					
	Blood draw for immunogenicity	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
	Collect blood sample for PBMC isolation[b]	~120 mL	~120 mL	~120 mL	~120 mL		

Abbreviations: HLA = human leukocyte antigen; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

a. Only for those participants randomized to receive a second dose of BNT162b2 OMI as part of Substudy D.
b. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 401) for select participants at select sites only. See Section 10.10.8.2

10.10.1.2.2. Participants in Cohort 2

Cohort	Visit Number	401	402	404	404a	404b	404c	405	406
	Visit Description	**SSD Vaccination 1**	**1-Month Follow-Up Visit**	**3-Month Follow-Up Visit and 2nd SSD Vaccination**	**7-Day Follow-Up Visit After 2nd SSD Vaccination[a]**	**1-Month Follow-Up Visit After 2nd SSD Vaccination[a]**	**3-Month Follow-Up Visit After 2nd SSD Vaccination[a]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**
Cohort 2: Participants 18-55 years of age having received 3 doses of BNT162b2 before enrollment (3-6 months after last dose)	Group 3: (N=300)	BNT162b2 OMI 30-µg dose		BNT162b2 OMI 30-µg dose					
	Group 4: (N=300)	BNT162b2 30-µg dose		BNT162b2 OMI 30-µg dose					
	Blood draw for immunogenicity	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
	Collect blood sample for PBMC isolation[b]	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL		

Abbreviations: HLA = human leukocyte antigen; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

a. Only for those participants who consent to receive a dose of BNT162b2 OMI at Visit 404 as part of Substudy D.
b. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 401) for select participants at select sites only. See Section 10.10.8.2.

10.10.1.2.3. Participants in Cohort 3

	Visit Number	501	502	503	504	505	506	507	508
	Visit Description	**Vaccination 1**	**Vaccination 2 3 Weeks After Vaccination 1**	**1-Week Follow-Up Visit After Vaccination 2[a]**	**1-Month Follow-Up Visit After Vaccination 2**	**3-Month Follow-Up Visit After Vaccination 2**	**6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3[b]**	**1-Month Follow-Up Visit After Vaccination 3**	**6-Month Follow-Up Visit After Vaccination 3**
Cohort 3: COVID-19 vaccine–naive participants 18-55 years of age	Group 5: (N=205)	BNT162b2 OMI 30-µg dose	BNT162b2 OMI 30-µg dose				BNT162b2 30-µg dose		
	Blood draw for immunogenicity	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
	Collect blood sample for PBMC isolation[c]	~120 mL		~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL

Abbreviations: HLA = human leukocyte antigen; PBMC = peripheral blood mononuclear cell.

a. Only for those participants who are part of the group for description of cell-mediated immune response.
b. Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
c. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 501) for select participants at select sites only. See Section 10.10.8.2.

10.10.1.3. Schedule of Activities for Substudy D

10.10.1.3.1. Cohort 1

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After Last SSD Vaccination**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**28 to 35 Days After Visit 402**	**85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2				
Obtain informed consent	X						
Obtain the participant's prior study and participant number (if applicable)	X						
Confirm participant's past BNT162b2 experience (3-8 months since the last dose)	X						
Obtain demography and medical history data	X						
Perform clinical assessment[d]	X						
Measure height and weight	X						
Measure temperature (body)	X	X[b]					
Perform urine pregnancy test (if appropriate)	X	X[b]					

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After Last SSD Vaccination**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**28 to 35 Days After Visit 402**	**85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2				
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X		
For participants who are HIV-positive, record the latest CD4 count and HIV viral load	X	X		X	X	X	
Confirm eligibility	X	X[b]					
Review temporary delay criteria	X	X[b]					
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[e]	~120 mL	~120 mL	~120 mL	~120 mL			
Collect blood sample for HLA typing[e]	~5 mL						

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After Last SSD Vaccination**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**28 to 35 Days After Visit 402**	**85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2				
Obtain nasal (midturbinate) swab(s)	X	X[b]					X
Obtain randomization number and study intervention allocation using the IRT system	X						
Administer study intervention	X	X[b]					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X[b]					
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X	X					

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After Last SSD Vaccination**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**28 to 35 Days After Visit 402**	**85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2				
Provide/ensure the participant has a thermometer and measuring device	X	X[b]					
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[f]	X[f]	X[f]	X[f]
Collect e-diary or assist the participant to delete application						X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Visit Number	401	402	403	404	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1 and SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After Last SSD Vaccination**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**28 to 35 Days After Visit 402**	**85 to 95 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**175 to 189 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 402 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
			ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2				
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. Only for those participants randomized to receive a second dose of BNT162b2 OMI as part of Substudy D.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Including, if indicated, a physical examination.
e. Additional 120 mL for PBMC isolation and 5 mL for HLA typing for select participants at select sites only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.10.1.3.2. Cohort 2

Visit Number	401	402	404	404a	404b	404c	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1**	**3-Month Follow-Up Visit and 2nd SSD Vaccination[b]**	**7-Day Follow-Up Visit After SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After SSD Vax 2[b]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2[d]**	**5 to 9 Days After Visit 404**	**28 to 35 Days After Visit 404**	**85 to 95 Days After Visit 404**	**175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2								
Obtain informed consent	X		X[b]						
Obtain the participant's prior study and participant number (if applicable)	X								
Confirm participant's past BNT162b2 experience (3-8 months since the last dose)	X								
Obtain demography and medical history data	X								
Perform clinical assessment[e]	X								
Measure height and weight	X								
Measure temperature (body)	X		X[b]						

Visit Number	401	402	404	404a	404b	404c	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1**	**3-Month Follow-Up Visit and 2nd SSD Vaccination[b]**	**7-Day Follow-Up Visit After SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After SSD Vax 2[b]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2[d]**	**5 to 9 Days After Visit 404**	**28 to 35 Days After Visit 404**	**85 to 95 Days After Visit 404**	**175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
				ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Perform urine pregnancy test (if appropriate)	X		X[b]						
Confirm use of contraceptives (if appropriate)	X	X	X[b]	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X	X
Collect nonstudy vaccine information	X	X	X	X	X	X	X		
For participants who are HIV-positive, record the latest CD4 count and HIV viral load	X	X	X		X	X	X	X	
Confirm eligibility	X		X[b]						
Review temporary delay criteria	X		X[b]						
Collect blood sample for immunogenicity assessment	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	

Visit Number	401	402	404	404a	404b	404c	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1**	**3-Month Follow-Up Visit and 2nd SSD Vaccination[b]**	**7-Day Follow-Up Visit After SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After SSD Vax 2[b]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2[d]**	**5 to 9 Days After Visit 404**	**28 to 35 Days After Visit 404**	**85 to 95 Days After Visit 404**	**175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
				ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Collect blood sample for PBMC isolation[f]	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL			
Collect blood sample for HLA typing[f]	~5 mL								
Obtain nasal (midturbinate) swab(s)	X		X[b]						X
Obtain randomization number and study intervention allocation using the IRT system	X								
Administer study intervention	X		X[b]						
Assess acute reactions for at least 30 minutes after study intervention administration	X		X[b]						

Visit Number	401	402	404	404a	404b	404c	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1**	**3-Month Follow-Up Visit and 2nd SSD Vaccination[b]**	**7-Day Follow-Up Visit After SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After SSD Vax 2[b]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2[d]**	**5 to 9 Days After Visit 404**	**28 to 35 Days After Visit 404**	**85 to 95 Days After Visit 404**	**175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
				ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X		X[b]						
Provide/ensure the participant has a thermometer and measuring device	X		X[b]						

Visit Number	401	402	404	404a	404b	404c	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1**	**3-Month Follow-Up Visit and 2nd SSD Vaccination[b]**	**7-Day Follow-Up Visit After SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After SSD Vax 2[b]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2[d]**	**5 to 9 Days After Visit 404**	**28 to 35 Days After Visit 404**	**85 to 95 Days After Visit 404**	**175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
				ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
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	X				
Collect AEs and SAEs as appropriate	X	X	X[g]	X	X	X[g]	X[g]	X[g]	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

Visit Number	401	402	404	404a	404b	404c	405	406	Unplanned
Visit Description	**SSD Vaccination 1[a]**	**1-Month Follow-Up Visit After SSD Vax 1**	**3-Month Follow-Up Visit and 2nd SSD Vaccination[b]**	**7-Day Follow-Up Visit After SSD Vax 2[b]**	**1-Month Follow-Up Visit After SSD Vax 2[b]**	**3-Month Follow-Up Visit After SSD Vax 2[b]**	**6-Month Follow-Up Visit After Last SSD Vaccination**	**12-Month Follow-Up Visit After Last SSD Vaccination**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 401**	**85 to 95 Days After Visit 401 or 85 to 123 Days for Participants Receiving SSD Vax 2[d]**	**5 to 9 Days After Visit 404**	**28 to 35 Days After Visit 404**	**85 to 95 Days After Visit 404**	**175 to 189 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**350 to 378 Days After Visit 401 (or After Visit 404 for Participants Who Received SSD Vax 2)**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
				ONLY FOR THE PARTICIPANTS WHO RECEIVE SSD VACCINATION 2					
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; SSD = Substudy D.

a. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
b. Only for those participants who consent to receive a dose of BNT162b2 OMI at Visit 404 as part of Substudy D.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. For those participants who consent to receive a second dose of BNT162b2 OMI as part of Substudy D, the Visit 3 window is 85 to 123 days.
e. Including, if indicated, a physical examination.
f. Additional 120 mL for PBMC isolation and 5 mL for HLA typing for select participants at select sites only.
g. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.10.1.3.3. Cohort 3

Visit Number	501	502	503	504	505	506	507	508	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-Up Visit After Vaccination 2[a]**	**1-Month Follow-Up Visit After Vaccination 2**	**3-Month Follow-Up Visit After Vaccination 2**	**6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3[b]**	**1-Month Follow-Up Visit After Vaccination 3**	**6-Month Follow-Up Visit After Vaccination 3**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1[d]**	**19 to 23 Days After Visit 501**	**6 to 8 Days After Visit 502**	**28 to 35 Days After Visit 502**	**85 to 95 Days After Visit 502**	**150 to 199 Days After Visit 502**	**28 to 35 Days After Visit 506**	**175 to 189 Days After Visit 506**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain informed consent	X								
Assign participant number	X								
Obtain demography and medical history data	X								
Perform clinical assessment[e]	X								
Measure height and weight	X								
Measure temperature (body)	X	X				X			
Perform urine pregnancy test (if appropriate)	X	X				X			
Confirm use of contraceptives (if appropriate)	X	X	X	X		X	X		
Collect nonstudy vaccine information	X	X	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X			X	X	X	X	X	
Confirm eligibility	X	X				X			
Review temporary delay criteria	X	X				X			
Collect blood sample for immunogenicity assessment	~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[f]	~120 mL		~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	~120 mL	
Collect blood sample for HLA typing[f]	~5 mL								

Visit Number	501	502	503	504	505	506	507	508	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-Up Visit After Vaccination 2[a]**	**1-Month Follow-Up Visit After Vaccination 2**	**3-Month Follow-Up Visit After Vaccination 2**	**6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3[b]**	**1-Month Follow-Up Visit After Vaccination 3**	**6-Month Follow-Up Visit After Vaccination 3**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1[d]**	**19 to 23 Days After Visit 501**	**6 to 8 Days After Visit 502**	**28 to 35 Days After Visit 502**	**85 to 95 Days After Visit 502**	**150 to 199 Days After Visit 502**	**28 to 35 Days After Visit 506**	**175 to 189 Days After Visit 506**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Obtain nasal (midturbinate) swab	X	X				X			X
Obtain the participant's vaccine vial allocation using the IRT system	X	X				X			
Administer study intervention	X	X				X[b]			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				X			
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X	X				X			
Provide/ensure the participant has a thermometer and measuring device	X	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			X		
Collect AEs and SAEs as appropriate	X	X	X	X	X[g]	X	X	X[g]	X
Collect e-diary or assist the participant to delete application								X	

Visit Number	501	502	503	504	505	506	507	508	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Week Follow-Up Visit After Vaccination 2[a]**	**1-Month Follow-Up Visit After Vaccination 2**	**3-Month Follow-Up Visit After Vaccination 2**	**6-Month Follow-Up Visit After Vaccination 2 and Administration of Vaccination 3[b]**	**1-Month Follow-Up Visit After Vaccination 3**	**6-Month Follow-Up Visit After Vaccination 3**	**Potential COVID-19 Illness Visit[c]**
Visit Window (Days)	**Day 1[d]**	**19 to 23 Days After Visit 501**	**6 to 8 Days After Visit 502**	**28 to 35 Days After Visit 502**	**85 to 95 Days After Visit 502**	**150 to 199 Days After Visit 502**	**28 to 35 Days After Visit 506**	**175 to 189 Days After Visit 506**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)									X
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X	X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell.

a. Only for those participants who are part of the group for description of cell-mediated immune response.
b. Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
e. Including, if indicated, a physical examination.
f. Additional 120 mL for PBMC isolation and 5 mL for HLA typing is for select participants at select sites only.
g. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.10.2. Introduction

10.10.2.1. Study Rationale

On 24 November 2021, South Africa reported the identification of a new SARS-CoV-2 variant, B.1.1.529, to the WHO. On 26 November 2021 and 30 November 2021, the WHO and the US, respectively, classified this new variant as a VOC and named it Omicron. The Omicron variant has also been detected in several European countries, as well as in North/South America, Asia, and Australia.[44]

The Omicron variant has many concerning spike protein mutations, some of which are known from other variants to be associated with reduced neutralization by convalescent and vaccine sera. Specific characteristics unique to Omicron are that the spike protein is characterized by at least 30 amino acid substitutions, 3 small deletions, and 1 small insertion. Notably, 15 of the 30 amino acid substitutions are in the receptor-binding domain. There are also a number of changes and deletions in other genomic regions.[23]

In regard to transmissibility, it is currently unknown how efficiently Omicron can spread from person to person. The replacement of Delta by Omicron as the predominant variant in South Africa raises concerns that it may be more transmissible than Delta, but because of the low number of cases in South Africa when it emerged, it is unclear if this variant is more transmissible than the Delta variant. Analysis of the changes in the spike protein indicate that Omicron is likely to have increased transmission compared to the original SARS-CoV-2 virus, but it is difficult to infer if it is more transmissible than Delta. In addition, it is unclear if infection with Omicron is associated with more severe disease. Lastly, to date there are no published data available to assess the ability of sera from vaccinated persons or those with previous SARS-CoV-2 infection to neutralize the Omicron variant.[23] Laboratory and epidemiological studies are needed to assess the impact of the Omicron variant on vaccine effectiveness and breakthrough infections, including in individuals who have received booster doses.[23]

Pfizer has developed a new vaccine, BNT162b2 OMICRON (B.1.1.529), which is a BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron B.1.1.529 variant-specific mutations. This new vaccine will be utilized in Substudy D. Substudy D has been designed to assess the safety, tolerability, and immunogenicity of BNT162b2 OMI within 3 different cohorts: 1) participants who have previously received 2 doses of BNT162b2 and will receive either 1 dose of BNT162b2 or 1 or 2 doses of BNT162b2 OMI; 2) participants who have previously received 3 doses of BNT162b2 and will receive a fourth dose of either BNT162b2 or BNT162b2 OMI (participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up); and 3) participants who are BNT162b2-naïve and will receive 2 doses of BNT162b2 OMI, followed by a dose of BNT162b2.

See Section 2.2 for the study background.

10.10.2.2. Benefit/Risk Assessment

No additional risks are identified for Substudy D beyond those detailed for the master study (see Section 2.3).

10.10.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy D may be:

- Receipt of a third, fourth, or fifth dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic.

- Contributing to research to help others in a time of global pandemic.

10.10.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
• To describe the safety and tolerability profile of BNT162b2 OMI given as the third, fourth, or fifth dose to BNT162b2-experienced participants, or as a 2-dose series to COVID-19 vaccine–naïve participants • To describe the safety and tolerability profile of BNT162b2 given as a third or fourth dose to BNT162b2-experienced participants (Group 2b, Group 4, and Group 5)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from the first study vaccination (received in this study) through 1 month after the last study vaccination • SAEs from the first study vaccination (received in this study) through 6 months after the last study vaccination	• 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
Primary Immunogenicity ***BNT162b2-experienced participants***		
G1vG2bA: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
G2vG2bA: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 2 doses of BNT162b2 OMI given as the third and fourth doses compared to after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 or 2 doses of intervention as appropriate) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 2 doses of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the third (and fourth) dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 2 doses of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the third (and fourth) dose in BNT162b2-experienced participants	SARS-CoV-2 Omicron-neutralizing titers
G3vG4A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
COVID-19 vaccine–naïve participants		
G5A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 2 doses of BNT162b2 OMI compared to after 2 doses of BNT162b2 in age-matched participants randomly selected from the C4591001 study	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2 OMI or BNT162b2 as appropriate) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers 1 month after the second dose of BNT162b2 OMI to 1 month after the second dose of BNT162b2 in age-matched participants randomly selected from the C4591001 study • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after the second dose of BNT162b2 OMI and at 1 month after the second dose of BNT162b2 in age-matched participants randomly selected from the C4591001 study	SARS-CoV-2 Omicron-neutralizing titers
Secondary Immunogenicity ***BNT162b2-experienced participants***		
G1vG2bB: To demonstrate the "super" superiority of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	Same as GMR estimand of G1vG2bA	Same as G1vG2bA
G2vG2bB: To demonstrate the "super" superiority of the anti-Omicron immune response after 2 doses of BNT162b2 OMI given as the third and fourth doses compared to after 1 dose of BNT162b2 given as the third dose in BNT162b2-experienced participants	Same as GMR estimand of G2vG2bA	Same as G2vG2bA
G3vG4B: To demonstrate the "super" superiority of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	Same as GMR estimand of G3vG4A	Same as G3vG4A

Objectives	Estimands	Endpoints
COVID-19 vaccine–naïve participants		
G5B: To demonstrate the noninferiority of the anti-Omicron immune response after 2 doses of BNT162b2 OMI compared to the anti–reference-strain immune response after 2 doses of BNT162b2 in age-matched participants randomly selected from the C4591001 study	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2 OMI or BNT162b2 as appropriate) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers 1 month after the second dose of BNT162b2 OMI to the reference-strain–neutralizing titers 1 month after the second dose of BNT162b2 in age-matched participants randomly selected from the C4591001 study • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after the second dose of BNT162b2 OMI and seroresponse[a] to the reference strain at 1 month after the second dose of BNT162b2 in age-matched participants randomly selected from the C4591001 study	SARS-CoV-2 Omicron- and reference-neutralizing titers
G5C: To demonstrate the "super" superiority of the anti-Omicron immune response after 2 doses of BNT162b2 OMI compared to after 2 doses of BNT162b2 in age-matched participants randomly selected from the C4591001 study	Same as GMR estimand of G5A	Same as G5A
Exploratory		
To describe the immune response to BNT162b2 OMI or BNT162b2 given as the third and/or fourth and/or fifth dose in BNT162b2-experienced participants	• GMT at each time point • GMFRs from before the first dose of study intervention to subsequent time points • Percentages of participants with seroresponse[a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
To describe the immune response to BNT162b2 OMI in COVID-19 vaccine–naïve participants	• GMT at each time point • GMFRs from before the first dose of BNT162b2 OMI to subsequent time points • Percentages of participants with seroresponse[a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
To describe the immune response to the reference strain and VOCs in a subset of 30 participants[b] per group		• SARS-CoV-2 neutralizing titers for the reference strain and VOCs
To describe the immune response to any VOCs not already specified (eg, Delta)		• SARS-CoV-2 neutralizing titers for any VOCs not already specified (eg, Delta)
To describe confirmed COVID-19 and severe COVID-19 cases		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases

Objectives	Estimands	Endpoints
		• Strain sequencing of COVID-19 cases
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group		

a. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. This subset of participants will not contribute to the assessment of primary and secondary immunogenicity objectives.

10.10.4. Study Design

10.10.4.1. Overall Design

This is a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose primary series of BNT162b2 OMI, and as a booster (third, fourth, or fifth) dose at investigator sites in the US and South Africa only. Participants ≥18 years of age to ≤55 years of age will be enrolled. Approximately 1420 participants will be enrolled in the study.

Participants in Cohort 1 will have completed a 2-dose primary series of BNT162b2 (30-µg doses), with their last dose 90 to 240 days prior to enrollment. Approximately 615 participants will be randomized at a ratio of 1:1:1 either to receive 1 dose (third) of BNT162b2 OMI, 2 doses (third and fourth) of BNT162b2 OMI, 4 weeks apart, or 1 dose (third) of BNT162b2. Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose, but the investigator and sponsor will not be blinded.

Participants in Cohort 2 will be enrolled from Study C4591001 and C4591031 Substudy A and will have completed a 2-dose primary series and received a single booster (third) dose of BNT162b2, with their last dose 90 to 180 days prior to randomization. Approximately 600 participants will be randomized at a ratio of 1:1 to receive a fourth dose of either BNT162b2 or BNT162b2 OMI at Visit 401. Participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Randomization will be stratified by age (stratified as 18-30 and 31-55 years of age). Cohort 2 will be observer-blinded.

In Cohort 3, 205 participants 18 through 55 years of age who are COVID-19 vaccine–naïve and have not experienced COVID-19 will be enrolled to receive 2 doses (primary series) of BNT162b2 OMI, 3 weeks apart, with a dose of BNT162b2 approximately 5 months later. If participants do not consent to receive BNT162b2 as a third dose, they will not receive a third dose. No participants should receive BNT162b2 OMI as a third dose.

A subset of 30 participants may be selected from each group to serve as a sentinel group for immunogenicity assessment. Participants in the subset will not contribute to the assessment of primary and secondary immunogenicity objectives. Immunogenicity data from these participants will be summarized separately for the exploratory objective specific for the subset. See Section 10.10.9.5 for details.

Table 11 details the number of participants by cohort and group, their prior BNT162b2 experience, the vaccine that will be administered, and the number of doses administered as part of Substudy D.

Table 11. Total Number of Participants by Cohort

Cohort	Group	Prior BNT162b2 Experience	Vaccine	Number of Doses Administered as Part of Substudy D	Total Number of Participants
Cohort 1	Group 1	2 Doses	BNT162b2 OMI	1	205
	Group 2	2 Doses	BNT162b2 OMI	2	205
	Group 2b	2 Doses	BNT162b2	1	205
Cohort 2	Group 3	3 Doses	BNT162b2 OMI	1 or 2	300
	Group 4	3 Doses	BNT162b2 (and BNT162b2 OMI at Visit 404)	1 or 2	300
Cohort 3	Group 5	Naïve	BNT162b2 OMI	2	205
			BNT162b2	1	

Note: Cohorts 1 and 2 are observer-blinded. Participants in Cohort 1 will remain blinded to whether they will be receiving a fourth dose through 1 month after their first dose. Cohort 2 participants will be unblinded once they have completed Visit 404. Cohort 3 is open-labeled.

10.10.4.2. Scientific Rationale for Substudy D Design

See Section 10.10.2.1.

10.10.4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

10.10.4.3. Justification for Dose

See Section 4.3 for a justification of the BNT162b2 and BNT162b2 OMI dose used in Substudy D.

10.10.4.4. End of Study Definition

See Section 4.4.

10.10.5. Study Population

Details of the master and Substudy D eligibility criteria are shown in Section 5. Participants must meet all of the general inclusion and exclusion criteria as specified for the master protocol as well as Substudy D–specific inclusion and exclusion criteria.

10.10.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants 18 to 55 years of age inclusive:

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

Type of Participant and Disease Characteristics:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.15.

4. Cohort 2: Participants who provided a serum sample at Visit 3 in Study C4591001, with Visit 3 occurring within the protocol-specified window.

Informed Consent:

5. 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.

Other Inclusions:

6. Cohort 1: Participants who have received 2 prior doses of 30 µg BNT162b2, with the second dose being 90 to 240 days before Visit 401 (Day 1)

   or

   Cohort 2: Participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being 90 to 180 days before Visit 401 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

10.10.5.2. Exclusion Criteria

Participants are excluded from Substudy D 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. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

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

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

6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. **Cohorts 1 and 2**: prior receipt of any COVID-19 vaccine other than BNT162b2.

10. **Cohort 3 only:** prior receipt of any COVID-19 vaccine.

Other Exclusions:

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

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

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

10.10.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy D as detailed in Section 5.3 and Section 10.4.

10.10.5.4. Screen Failures

See Section 5.4.

10.10.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.10.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

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

10.10.6.1. Study Intervention(s) Administered

See Section 6.1 for details of BNT162b2.

Additional Intervention Name	BNT162b2 OMICRON (B.1.1.529) (BNT162 RNA-LNP vaccine utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	30 µg
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP	IMP
Sourcing	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.

10.10.6.1.1. Administration

For Cohorts 1 and 2, participants will receive 1 dose of study intervention as allocated by the IRT at Visit 401 (third or fourth dose) in accordance with the substudy's SoA (Section 10.10.1.3). Group 2 participants will receive a second dose of BNT162b2 OMI at Visit 402. Group 3 and Group 4 participants may receive a dose of BNT162b2 OMI at Visit 404.

For Cohort 3, COVID-19 vaccine–naïve participants will receive 1 dose of BNT162b2 OMI at Visit 501 and Visit 502, and 1 dose of BNT162b2 at Visit 506. Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.

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

10.10.6.1.2. Preparation and Dispensing

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure that the participants in Cohorts 1 and 2 remain blinded. Cohort 3 is open-labeled.

10.10.6.2. Measures to Minimize Bias: Randomization and Blinding

10.10.6.2.1. Blinding of Site Personnel

In Cohort 1 (Groups 1 and 2b) and Cohort 2, 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.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The group of participants who will be enrolled to receive a third and fourth dose of BNT162b2 OMI (Group 2 of Cohort 1) will remain blinded to whether they will be receiving a fourth dose, through 1 month after their first dose of BNT162b2 OMI, but the investigator and sponsor will not be blinded.

Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1).

10.10.6.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation for Cohort 1 (Groups 1 and 2b) and Cohort 2. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 10.9.9.4.2). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

Participants in Cohort 1 (Groups 1 and 2b) may be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1). Cohort 2 participants will be unblinded once they have completed Visit 404. Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

10.10.6.2.3. 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.

10.10.6.3. Study Intervention Compliance

See Section 6.4.

10.10.6.4. Dose Modification

See Section 6.5.

10.10.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.10.6.6. Treatment of Overdose

See Section 6.7.

10.10.6.7. Concomitant Therapy

See Section 6.8.

10.10.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.10.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 250 mL for those participants who receive 1 dose and 300 mL for those who receive 2 doses. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 735 mL for those participants who receive 1 dose and 785 mL for those who receive 2 doses.

For those participants enrolled in Cohort 3, COVID-19 vaccine–naïve participants who will receive 2 doses of BNT162b2 OMI followed by 1 dose of BNT162b2, the total blood sampling volume for individual participants is up to approximately 350 mL. Those participants in the cohort who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 1195 mL.

For all participants, 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.

10.10.8.1. Surveillance for COVID-19

If, at any time, a participant develops acute respiratory illness (see Section 10.7.8.5.5.1), for the purposes of the study he or she will be considered to potentially have COVID-19 illness. In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA-approved under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (ie, NAAT) to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 10.7.8.5.5.1) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
    - Fever;
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste or smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
- Confirmed severe COVID-19 (FDA definition[45]): confirmed COVID-19 and presence of at least 1 of the following:
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
    - Significant acute renal, hepatic, or neurologic dysfunction;
    - Admission to an ICU;
    - Death.

- Confirmed severe COVID-19 (CDC definition[46]): confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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

10.10.8.2. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The test to be performed will be the SARS-CoV-2 neutralizing assay (reference strain and Omicron strain). Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each group for evaluation of boostability and protection against Omicron and the reference strain (both BNT162b2-experienced and BNT162b2-naïve) at select sites for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses to Omicron and the reference strain. A blood sample of ~5 mL for HLA typing will also be obtained.

10.10.8.3. Safety Assessments

See Section 8.2.

10.10.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.10.8.5. Specified Genetics

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

See Appendix 16 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

10.10.8.6. Substudy D Procedures

10.10.8.6.1. Administration of Additional Dose(s) of BNT162b2 or BNT162b2 OMI (Cohort 1)

10.10.8.6.1.1. Visit 401 – Substudy D Vaccination (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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).

As Cohort 1 is observer-blinded, the blinded and unblinded roles should still be maintained to ensure the integrity of the blind:

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- 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.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.2.4), 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 reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.10.8.6.4 for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.6.7).
- 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 10.10.8.6.4.1.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the reactogenicity 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.

10.10.8.6.1.2. Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401)

- 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 6.8.

- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.

Only if the participant is to receive a second dose of BNT162b2 OMI (Substudy D Vaccination 2):

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Measure the participant's body temperature.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

  Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see Section 7.1.
- 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 BNT162b2 OMI 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 has a self-swab kit.
- Remind the participant of the e-diary technologies available for this study (see Section 10.10.8.6.5). Provide instructions on e-diary completion and ask the

participant to complete the reactogenicity e-diary from Day 1 through 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 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 10.10.8.6.8):
    - 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- 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.
- 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.

10.10.8.6.1.3. Visit 403 – 1-Month Follow-Up Visit (After Substudy D Vaccination 2) (28 to 35 Days After Visit 402): Only for Those Participants Who Receive Substudy D Vaccination 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 6.8.

- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.1.4. Visit 404 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 401, or 85 to 95 Days After Visit 402 for Those Participants Who Receive Substudy D Vaccination 2)

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.

- 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.
- Participants in Cohort 1 (Groups 1 and 2b) may be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1). Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

10.10.8.6.1.5. Visit 405 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 401, or 175 to 189 Days After Visit 402 for Those Participants Who Receive Substudy D Vaccination 2)

- Record AEs as described in Section 8.3
- Collect a blood sample for immunogenicity testing.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.1.6. Visit 406 – 12-Month Follow-Up Visit (350 to 378 Days After Visit 401, or 350 to 378 Days After Visit 402 for Those Participants Who Receive Substudy D Vaccination 2)

- Collect a blood sample for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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.

10.10.8.6.2. Administration of Additional Dose(s) of BNT162b2 or BNT162b2 OMI (Cohort 2)

Participants who do not provide consent to receive a dose of BNT162b2 OMI at Visit 404 will remain on the single-dose visit schedule.

10.10.8.6.2.1. Visit 401 – Substudy D Vaccination (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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).

As Cohort 2 is observer-blinded, the blinded and unblinded roles should still be maintained to ensure the integrity of the blind:

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- 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.

- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.2.4), 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 reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.10.8.6.4 for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.6.7).

- 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 10.10.8.6.4.1.

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

10.10.8.6.2.2. Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.3. Visit 404 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 401, or 85 to 123 Days After Visit 401 for Those Participants Who Consent to Receive Substudy D Vaccination 2)

NOTE: Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have **COMPLETED** Visit 404 (3 months after Substudy D Vaccination 1). Since these will be the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- 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.

Only if the participant consents to receive a dose of BNT162b2 OMI (Substudy D Vaccination 2):

NOTE: Voluntary, written, study-specific informed consent will be obtained from the participant before the participant receives a dose of BNT162b2 OMI at Visit 404. 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 the participant receives a dose of BNT162b2 OMI.

NOTE: Participants who do not provide consent to receive a dose of BNT162b2 OMI at Visit 404 will remain on the single-dose visit schedule.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Measure the participant's body temperature.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

  Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see Section 7.1.
- 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 BNT162b2 OMI 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 has a self-swab kit.

- Remind the participant of the e-diary technologies available for this study (see Section 10.10.8.6.5). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through 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 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 10.10.8.6.8):

  - 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.

- 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.

- 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.

- Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have completed Visit 404 (3 months after Substudy D Vaccination 1). Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.

10.10.8.6.2.4. Visit 404a – 7-Day Follow-Up Visit (After Substudy D Vaccination 2) (5 to 9 Days After Visit 404): Only for Those Participants Who Receive Substudy D Vaccination 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.6.7).
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.5. Visit 404b – 1-Month Follow-Up Visit (After Substudy D Vaccination 2) (28 to 35 Days After Visit 404): Only for Those Participants Who Receive Substudy D Vaccination 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.6. Visit 404c – 3-Month Follow-Up Visit (After Substudy D Vaccination 2) (85 to 95 Days After Visit 404): Only for Those Participants Who Receive Substudy D Vaccination 2

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Collect a blood sample for immunogenicity testing.

- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.7. Visit 405 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 401, or 175 to 189 Days After Visit 404 for Those Participants Who Receive Substudy D Vaccination 2)

- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.2.8. Visit 406 – 12-Month Follow-Up Visit (350 to 378 Days After Visit 401, or 350 to 378 Days After Visit 404 for Those Participants Who Receive Substudy D Vaccination 2)

- Collect a blood sample for immunogenicity testing.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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.

10.10.8.6.3. Administration of BNT162b2 OMI to COVID-19 Vaccine–Naïve Participants (Cohort 3)

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new group of participants will be enrolled who are COVID-19 vaccine-naïve and have not experienced COVID-19. They will receive 2 doses (primary series) of BNT162b2 OMI, separated by 21 days, with a third dose approximately 5 months later.

10.10.8.6.3.1. Visit 501 – 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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

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

- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2 OMI into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 10.10.8.6.5), 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 reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.10.8.6.4 for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.6.7).

- 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 10.10.8.6.4.1.

- 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 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.

10.10.8.6.3.2. Visit 502 – Vaccination 2 (19 to 23 Days After Visit 501)

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 5.3.

- Record nonstudy vaccinations as described in Section 6.8.

- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see Section 10.10.5).

  Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please 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 10.10.5.5.

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

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2 OMI into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

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

- 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 the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.6.7).

- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.

- Ensure the participant has a self-swab kit.

- 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 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.

10.10.8.6.3.3. Visit 503 – 1-Week Follow-Up Visit (After Vaccination 2) (6 to 8 Days After Visit 502): Only for Those Participants Who Are Part of the Group for Description of Cell-Mediated Immune Response

- Record AEs as described in Section 8.3

- Record nonstudy vaccinations as described in Section 6.8.

- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.

- Discuss contraceptive use as described in Section 5.3.

- Collect a blood sample for immunogenicity testing.

- Collect a blood sample (approximately 120 mL) for PBMC isolation.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.6.7).

- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.

- Ensure the participant has a self-swab kit.

- 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.

10.10.8.6.3.4. Visit 504 – 1-Month Follow-Up Visit (After Vaccination 2) (28 to 35 Days After Visit 502)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.3.5. Visit 505 – 3-Month Follow-Up Visit (After Vaccination 2) (85 to 95 Days After Visit 502)

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.8.

- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.10.8.6.4.1
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.3.6. Visit 506 – 6-Month Follow-Up Visit (After Vaccination 2) (150 to 199 Days After Visit 502) and Administration of Vaccination 3

- Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Measure the participant's body temperature.

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

  Note: a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (based on signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. Please see Section 7.1.

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

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

- Obtain the participant's vaccine vial allocation using the IRT system.

- 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. Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.

- 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.

- Remind the participant of the e-diary technologies available for this study (see Section 10.10.8.6.5). Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through 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 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 10.8.8.3.7):

  - 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 10.10.8.6.4.1.
- Ensure the participant has a self-swab kit.
- 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.

10.10.8.6.3.7. Visit 507 – 1-Month Follow-Up Visit (After Vaccination 3) (28 to 35 Days After Visit 506)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.10.8.6.4.1.

- Ensure the participant has a self-swab kit.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

10.10.8.6.3.8. Visit 508 – 6-Month Follow-Up Visit (After Vaccination 3) (175 to 189 Days After Visit 506)

- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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.

10.10.8.6.4. COVID-19 Surveillance (All Substudy D Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 10.10.8.6.5) 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.

10.10.8.6.4.1. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

    - Significant acute renal, hepatic, or neurologic dysfunction

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)

  - Clinical diagnosis

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

  - Full blood count

  - Blood chemistry, specifically creatinine, urea, LFTs, and C-reactive protein

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay

  - Death

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

10.10.8.6.5. 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 the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

10.10.8.6.6. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 401, 402 (for Group 2 participants who receive a second dose of BNT162b2 OMI only), 404 (for Group 3 and Group 4 participants who receive a dose of BNT162b2 OMI at Visit 404 only), 501, 502, and 506: To determine whether a participant will be included in immunogenicity analyses of those with no serological or virological evidence (up to 1 month after receipt of the third, fourth, or fifth dose to BNT162b2-experienced participants, or as a 2-dose series to COVID-19 vaccine–naïve participants) of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 401 and Visit 501 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise

receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.10.8.6.7. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis. In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

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

If a Grade 3 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 that 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 8.2.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.4.3.
- 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.

10.10.9. Statistical Considerations for Substudy D

See Section 9 for master protocol statistical considerations and substudy specifics below.

10.10.9.1. Statistical Hypotheses

10.10.9.1.1. Estimands

The estimands corresponding to the primary and secondary objectives are described in the table in Section 10.10.3.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.10.9.1.2. Statistical Hypotheses

The primary immunogenicity objectives for each cohort are to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by BNT162b2 OMI relative to the anti-Omicron immune response elicited by BNT162b2. Each primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(1) corresponds to a 1-fold margin for superiority and

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after BNT162b2 OMI;

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after BNT162b2.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to the Omicron strain at 1 month after BNT162b2 OMI;

  - p_2 is the percentage of participants with seroresponse to the Omicron strain at 1 month after BNT162b2.

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Superiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

The secondary objectives of "super" superiority will be evaluated using a 1.5-fold margin for GMR. "Super" superiority for GMR will be established if the lower limit of the 2-sided 95% CI for the GMR is greater than 1.5.

The secondary objective of noninferiority of the anti-Omicron immune response induced by BNT162b2 OMI relative to the anti–reference-strain immune response elicited by BNT162b2 will be assessed using 1.5-fold noninferiority margin for GMR and 10% noninferiority margin for seroresponse rate difference.

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8; noninferiority based on seroresponse rate difference will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

10.10.9.1.3. Multiplicity Adjustment

The immunogenicity objectives for BNT162b2-experienced participants who completed a 2-dose primary series of BNT162b2 prior to enrollment in this study (Cohort 1), BNT162b2-experienced participants who completed a 2-dose primary series and a booster dose of BNT162b2 prior to enrollment in this study (Cohort 2), and COVID-19 vaccine–naïve participants (Cohort 3) will be evaluated independently. The 3 cohorts (2-dose BNT162b2-experienced, 3-dose BNT162b2-experienced, and COVID-19 vaccine–naïve individuals) are different populations with different objectives. The 3 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the immunogenicity assessments of the 3 populations.

For each population, the objectives will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

- Cohort 1 (Groups 1, 2, 2b): G2vG2bA → G1vG2bA → G2vG2bB → G1vG2bB
- Cohort 2 (Groups 3 and 4): G3vG4A → G3vG4B
- Cohort 3 (Group 5): G5A → G5B → G5C.

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference will be assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled for each of these 3 populations.

10.10.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention(s) to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized/assigned participants who receive at least 1 dose of the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive at least 1 dose of the study intervention.

10.10.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.10.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

10.10.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after the last study vaccination will be provided for each vaccine group.
Immunogenicity	For each primary immunogenicity estimand described in Section 10.10.3 • GMRs and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.2.3. • The percentages of participants with seroresponse for each group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (see Section 9.3.1.1). • For Cohorts 1 and 2, only participants with no serological or virological evidence (up to 1 month after receipt of 1 or 2 doses of study intervention as appropriate) of past SARS-CoV-2 infection will be included in the analysis. • Superiority based on GMR will be established if the lower bound of the 2-sided 95% CI for the GMR is >1. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -5%.

10.10.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	For each secondary immunogenicity estimand described in Section 10.10.3 • GMR and the associated 2-sided 95% CIs, the percentages of participants with seroresponse, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using same method as for the primary immunogenicity objectives. • Noninferiority and "super" superiority will be evaluated using criteria as described in Section 10.10.9.1.2 and Section 10.10.9.1.3.

10.10.9.3.4. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMTs and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers** **Percentages of participants with seroresponse to Omicron- or reference-strain** • GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from baseline (before the first study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. • The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. **GMTs and GMFRs of SARS-CoV-2 reference strain and VOCs for the subset of 30 participants per group** **Percentages of participants with seroresponse to reference strain and VOCs for the subset of 30 participants per group** • GMTs, GMFRs, and percentages of participants with seroresponse for the subset of 30 participants per group, along with the associated 95% CIs, will be calculated using same method as described above.

Endpoint	Statistical Analysis Methods
	GMTs for any VOCs not already specified, after any dose of BNT162b2 OMI or BNT162b2 • GMTs of VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs and GMRs of VOC-neutralizing titers to reference-strain–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.
Cell-mediated immune response	The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

10.10.9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

10.10.9.4.1. Analysis Timing

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

- Safety data through 1 month after the first study vaccination received in this study for Groups 1, 2b, 3, and 4 or through 1 month after the second study vaccination received in this study for Groups 2 and 5.
- Immunogenicity data for the subset of 30 participants per group.
- Immunogenicity data through 1 month after the first study vaccination (for Groups 1, 2b, 3, and 4) or 1 month after the second study vaccination (for Groups 2 and 5) received in this study for participants enrolled in this study and through 1 month after Dose 2 for the comparator group from the C4591001 study.
- Complete safety and immunogenicity analysis approximately 6 months after the last study vaccination for each group.
- Complete safety and immunogenicity analysis approximately 12 months after the last study vaccination for each group.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses conducted while the study is ongoing will be performed by an unblinded team.

10.10.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

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

10.10.9.5. Sample Size Determination

The sample size for Groups 3 and 4 is based on consideration of an acceptable safety database. A subset of 30 participants from each group may be selected as a sentinel group for separate assessment of immune response defined in an exploratory objective. The subset may be the first 30 participants selected for operational expedience or a random sample selection depending on the enrollment status. The remaining approximately 175 participants in each of Groups 1, 2, 2b, and 5, and a random sample of 175 participants from each of Groups 3 and 4 selected from the remaining approximately 270 participants, will be used for evaluation of the primary and secondary immunogenicity objectives in each group. The same number of age-matched participants for Group 5 will be selected from the C4591001 study as a control group for the immunogenicity evaluation.

Assuming a 35% nonevaluable and prior SARS-CoV-2 infection rate, approximately 114 evaluable participants in each group will contribute to the immunogenicity evaluation. The superiority and noninferiority evaluation based on GMR and seroresponse rate difference will each be performed at 1-sided alpha level of 0.025 as described in Section 10.10.9.1.3.

Superiority Immunogenicity Objectives

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose or 1 month after Dose 2 in log scale is assumed to be 0.93 based on data observed in the C4591001 study. If the true GMR of Omicron-neutralizing titer after BNT162b2 OMI to after BNT162b2 is 1.5, 114 evaluable participants per group will provide 90.6% power to declare superiority. If the true GMR is 2.5, the study will have 98.5% power to declare “super” superiority using a 1.5-fold margin.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 80% in the BNT162b2 OMI group and 60% in the BNT162b2 group, the study has 98.6% power to demonstrate noninferiority using a 5% margin.

Secondary Noninferiority Immunogenicity Objectives

For comparisons based on GMR, common assay standard deviations at 1 month after Dose 2 in log scale is assumed to be 0.93 based on data observed in the C4591001 study. A GMR of 1 is assumed for each comparison. For comparisons based on seroresponse, a 95% response rate is assumed for each comparative group at the comparative time point. With 114 evaluable participants and the stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has 89.9% power to demonstrate noninferiority based on GMR using a 1.5-fold margin and 85.8% power to declare noninferiority based on seroresponse rate using a 10% margin.

For safety outcomes, Table 12 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 1%, with 300 participants in a vaccine group, there is 95% probability of observing at least 1 AE.

Table 12. Probability of Observing at 1 Least AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=30	N=205	N=300	N=915	N=1420
0.01%	0.003	0.02	0.03	0.09	0.13
0.02%	0.006	0.04	0.06	0.17	0.25
0.05%	0.01	0.10	0.14	0.37	0.51
0.10%	0.03	0.19	0.26	0.60	0.76
0.20%	0.06	0.34	0.45	0.84	0.94
0.50%	0.14	0.64	0.78	0.99	>0.99
1.00%	0.26	0.87	0.95	>0.99	>0.99
2.00%	0.45	0.98	>0.99	>0.99	>0.99
5.00%	0.79	>0.99	>0.99	>0.99	>0.99
10.0%	0.96	>0.99	>0.99	>0.99	>0.99

10.11. Appendix 11: Substudy E

10.11.1. Substudy Summary

10.11.1.1. Substudy Synopsis

See Section 1.1 for a synopsis of Substudy E.

10.11.1.2. Schema

Visit Number	Screening	601	601A	602	603	604	605
Visit Description	**Screening[a]**	**4th Dose of BNT162b2, BNT162b2 OMI, or Combination BNT162b2 and BNT162b2 OMI**	**3 Days After 4th Vaccination[a]**	**7 Days After 4th Vaccination**	**1 Month After 4th Vaccination**	**3 Months After 4th Vaccination**	**6 Months After 4th Vaccination**
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		**ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9**				
Participants having received 3 prior doses of 30 µg BNT162b2 5-12 months prior to randomization		30-µg OR 60-µg dose					
Blood draw for immunogenicity assessment/PBMC isolation[b]		50 mL/120 mL		50 mL/120 mL	50 mL/120 mL	50 mL/120 mL	50 mL/120 mL
Blood draw for troponin levels	10 mL		10 mL				

a. Only for sentinel-cohort participants 18 to 55 years of age (Groups 7 to 9).
b. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 601) is for select expanded-enrollment participants (~30 per group for Groups 1 to 6, and ~90 across all groups for Groups 7 to 9) at select sites only. Sentinel-cohort participants will not have samples collected for PBMC isolation/HLA typing. See Section 10.11.8.2.

10.11.1.3. Schedule of Activities for Substudy E

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	**Screening[a]**	**Vaccination**	**3-Day Follow-Up Visit After Vaccination[a]**	**1-Week Follow-Up Visit After Vaccination**	**1-Month Follow-Up Visit After Vaccination**	**3-Month Follow-Up Visit After Vaccination**	**6-Month Follow-Up Visit After Vaccination**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**0 to 14 Days Before Visit 601**	**Day 1[c]**	**2 to 4 Days After Visit 601**	**6 to 8 Days After Visit 601**	**28 to 35 Days After Visit 601**	**85 to 95 Days After Visit 601**	**175 to 189 Days After Visit 601**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		**ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9**					
Obtain informed consent	X	X[d]						
Obtain the participant's prior study and participant number (if applicable)	X	X[d]						
Assign participant number	X	X[d]						
Obtain demography and medical history data	X	X[d]						
Perform clinical assessment[e]	X	X						
Measure height and weight	X	X						
Measure temperature (body)		X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X	X	X	
Collect prohibited medication use			X	X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X	X[d]			X	X	X	
Confirm eligibility	X	X						
Review temporary delay criteria		X						

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	**Screening[a]**	**Vaccination**	**3-Day Follow-Up Visit After Vaccination[a]**	**1-Week Follow-Up Visit After Vaccination**	**1-Month Follow-Up Visit After Vaccination**	**3-Month Follow-Up Visit After Vaccination**	**6-Month Follow-Up Visit After Vaccination**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**0 to 14 Days Before Visit 601**	**Day 1[c]**	**2 to 4 Days After Visit 601**	**6 to 8 Days After Visit 601**	**28 to 35 Days After Visit 601**	**85 to 95 Days After Visit 601**	**175 to 189 Days After Visit 601**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		**ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9**					
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL	~50 mL	
Collect blood sample for PBMC isolation[f]		~120 mL		~120 mL	~120 mL	~120 mL	~120 mL	
Collect blood sample for HLA typing[f]		~5 mL						
Collect a blood sample for troponin testing	10 mL		10 mL					
Obtain nasal (midturbinate) swab		X						X
Obtain the participant's vaccine vial allocation using the IRT system		X						
Administer study intervention		X						
Assess acute reactions for at least 30 minutes after study intervention administration		X						
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X						
Provide/ensure the participant has a thermometer and measuring device		X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		X→	X→	X→				

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	**Screening[a]**	**Vaccination**	**3-Day Follow-Up Visit After Vaccination[a]**	**1-Week Follow-Up Visit After Vaccination**	**1-Month Follow-Up Visit After Vaccination**	**3-Month Follow-Up Visit After Vaccination**	**6-Month Follow-Up Visit After Vaccination**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**0 to 14 Days Before Visit 601**	**Day 1[c]**	**2 to 4 Days After Visit 601**	**6 to 8 Days After Visit 601**	**28 to 35 Days After Visit 601**	**85 to 95 Days After Visit 601**	**175 to 189 Days After Visit 601**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		**ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9**					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates			X	X	X			
Collect AEs and SAEs as appropriate	X	X	X	X	X[g]	X[g]	X[g]	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

Visit Number	Screening	601	601A	602	603	604	605	Unplanned
Visit Description	**Screening[a]**	**Vaccination**	**3-Day Follow-Up Visit After Vaccination[a]**	**1-Week Follow-Up Visit After Vaccination**	**1-Month Follow-Up Visit After Vaccination**	**3-Month Follow-Up Visit After Vaccination**	**6-Month Follow-Up Visit After Vaccination**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**0 to 14 Days Before Visit 601**	**Day 1[c]**	**2 to 4 Days After Visit 601**	**6 to 8 Days After Visit 601**	**28 to 35 Days After Visit 601**	**85 to 95 Days After Visit 601**	**175 to 189 Days After Visit 601**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
	ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9		**ONLY FOR SENTINEL-COHORT PARTICIPANTS IN GROUPS 7, 8, AND 9**					
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs		X		X	X	X		

Abbreviations: HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell.

a. Only for sentinel-cohort participants 18 to 55 years of age in Groups 7 to 9. The Screening Visit can occur over more than 1 day.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
c. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
d. These Visit 601 procedures are not required for the Group 7, 8, and 9 sentinel-cohort participants, as they will be completed at the screening visit.
e. Including, if indicated, a physical examination.
f. Additional 120 mL for PBMC isolation (and 5 mL for HLA typing at Visit 601) is for select expanded-enrollment participants (~30 per group for Groups 1 to 6, and ~90 across all groups for Groups 7 to 9) at select sites only. Sentinel-cohort participants will not have samples collected for PBMC isolation/HLA typing. See Section 10.11.8.2.
g. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.11.2. Introduction

10.11.2.1. Study Rationale

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, is currently the dominant variant in many countries and within the US is responsible for 98.3% of sequenced COVID-19 cases as of 08 January 2022.[25] Current data note that the vaccine effectiveness against hospitalization is 88% (78%-93%) for Omicron after 3 doses of vaccine.[26] However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant. The addition of a higher dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile.[27] Therefore, Substudy E has been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

See Section 2.2 for the study background.

10.11.2.2. Benefit/Risk Assessment

A tolerability profile of a 60-µg dose of BNT162b2 has yet to be established. However, BNT162b1 (a candidate RNA-LNP vaccine tested in clinical trial C4591001 utilizing a nucleoside-modified messenger RNA similar to BNT162b2 but instead of encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein, BNT162b1 encodes the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain) was studied in adults 18 to 55 years of age at dose levels of 50 µg, 60 µg, and 100 µg. In one study, 60 participants were vaccinated with BNT162b1. Twelve participants for each of the dose level groups (1 µg, 10 µg, 30 µg, 50 µg, and 60 µg) were to receive the first dose on Day 1 and a second dose on Day 22. Due to the tolerability observed in participants after 2 doses of 50 µg and after reviewing the totality of the data available, including the local and systemic reactogenicity data (such as the increasing number of severe [Grade 3] systemic reactions reported with ascending dose), a second dose of 60 µg was not administered.[37,47] Another study investigated BNT162b1 at 10 µg, 30 µg, and 100 µg. Participants in this study were not administered the second dose of 100 µg because of the increased reactogenicity profile seen after a single dose at 100 µg and in participants who received 2 doses of 30 µg.[38] In light of better tolerability of BNT162b2 (compared to BNT162b1), and better tolerability in older adults (compared to younger adults), the potential benefit of a 60-µg dose of BNT162b2 is likely to outweigh the risk.

10.11.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy E may be:

- Receipt of a fourth dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic, particularly against new variant-associated infection and disease.

- Contributing to research to help others in a time of global pandemic.

10.11.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
• To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
• To describe the safety and tolerability profile of BNT162b2 OMI 60 µg and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants 18-55 years of age	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination • Percentage of participants with elevated troponin I levels before and 3 days after study vaccination (sentinel cohort only)	• 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 • Troponin I level (sentinel cohort only)
Primary Immunogenicity		
G3vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
G4vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
G5vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
G6vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers

Objectives	Estimands	Endpoints
Secondary Immunogenicity		
G5vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the reference strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 reference strain–neutralizing titers
G6vG1B: To demonstrate the noninferiority of anti–reference strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the reference strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 reference strain–neutralizing titers
To demonstrate the "super" superiority of anti-Omicron immune responses after 1 dose of BNT162b2 OMI at 30 µg (G3vG1B), BNT162b2 OMI at 60 µg (G4vG1B), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (G5vG1C), or bivalent BNT162b2 and BNT162b2 OMI at 60 µg (G6vG1C) compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	Same as GMR estimand of G3vG1A, G4vG1A, G5vG1A, G6vG1A	• SARS-CoV-2 Omicron-neutralizing titers
• **Exploratory**		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose in BNT162b2-experienced participants >55 years of age	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponse[a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference strain–neutralizing titers
To describe the immune response to bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg), BNT162b2 OMI 60 µg, and BNT162b2 30 µg[b] given as a fourth dose in BNT162b2-experienced participants 18 to 55 years of age	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponse[a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference strain–neutralizing titers

Objectives	Estimands	Endpoints
To describe the immune response to the reference strain and VOCs for participants[c] in sentinel cohorts of each age group		• SARS-CoV-2 neutralizing titers for the reference strain and VOCs
To describe the immune response to any VOCs not already specified in each age group		• SARS-CoV-2 neutralizing titers for any VOCs not already specified
To describe confirmed COVID-19 and severe COVID-19 cases in each age group		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group for each age group		

a. Seroresponse is defined as achieving ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. A subset of the youngest 150 participants from the >55-year-old group in Substudy E who have received bivalent BNT162b2 30 µg as a fourth dose will be selected for this objective.
c. This subset of participants will not contribute to the assessment of primary immunogenicity objectives.

10.11.4. Study Design

10.11.4.1. Overall Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose. Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization, will be enrolled at investigator sites in the US only. Participants >55 years of age will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 601 as a fourth dose. Participants 18 to 55 years of age will be randomized to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or BNT162b2 OMI at 60 µg at Visit 601 as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open-label) of 20 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 90 sentinel-cohort participants. An IRC will review all reported

AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 300 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

For participants 18 to 55 years of age, sentinel cohorts (sponsor open-label) of 30 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 15 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 75 sentinel-cohort participants. An IRC will review all reported AEs, reactogenicity e-diary data, and troponin levels from the sentinel cohorts collected through Day 7 to allow expanded enrollment upon confirmation of an acceptable safety assessment. An additional 900 participants will be enrolled and randomized in a 3:1:2 ratio to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg.

Table 13 and Table 14 describe the enrollment of the sentinel cohorts and steps to progress to expanded enrollment for the >55-year age groups and 18- to 55-year age groups, respectively.

Table 13. Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment

Initial-Sentinel Enrollment[a]		
Group	**Study Intervention**	**Number of Participants**
1	BNT162b2 30 µg (participants >55 years of age)	5
2	BNT162b2 60 µg (participants >55 years of age)	5
3	BNT162b2 OMI 30 µg (participants >55 years of age)	5
4	BNT162b2 OMI 60 µg (participants >55 years of age)	5
5	Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[b] (participants >55 years of age)	5
6	Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[b] (participants >55 years of age)	5
Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants		
Expanded-Sentinel Enrollment[a]		
Group	**Study Intervention**	**Number of Participants**
1	BNT162b2 30 µg (participants >55 years of age)	15
2	BNT162b2 60 µg (participants >55 years of age)	15
3	BNT162b2 OMI 30 µg (participants >55 years of age)	15
4	BNT162b2 OMI 60 µg (participants >55 years of age)	15
5	Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[b] (participants >55 years of age)	15
6	Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[b] (participants >55 years of age)	15
IRC review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.		
Expanded Enrollment[c]		
Group	**Study Intervention**	**Number of Participants**
1	BNT162b2 30 µg (participants >55 years of age)	300
2	BNT162b2 60 µg (participants >55 years of age)	300
3	BNT162b2 OMI 30 µg (participants >55 years of age)	300
4	BNT162b2 OMI 60 µg (participants >55 years of age)	300
5	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[d] (participants >55 years of age)	300
6	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[d] (participants >55 years of age)	300

Abbreviation: IRC = independent review committee.

a. Sentinel cohorts will be sponsor open-label.
b. Initial- and expanded-sentinel enrollment participants randomized to combination BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive doses that are prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine.
c. If the IRC's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
d. Expanded-enrollment participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required.

Table 14. Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment

Initial-Sentinel Enrollment[a,b]		
Group	**Study Intervention**	**Number of Participants**
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	5
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	5
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	5
Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants		
Expanded-Sentinel Enrollment		
Group	**Study Intervention**	**Number of Participants**
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	25
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	25
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	25
IRC review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.		
Expanded Enrollment[c]		
Group	**Study Intervention**	**Number of Participants**
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	450
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	150
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	300

Abbreviation: IRC = internal review committee.

a. Sentinel cohorts will be sponsor open-label.
b. Participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent ([Wild Type and Omicron [(B.1.1.529])] preformulated vaccine suspension for injection. No dilution is required.
c. If the IRC's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

10.11.4.2. Scientific Rationale for Substudy E Design

See Section 10.11.2.1.

10.11.4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the US population distribution (Census-based), to ensure that the study population is representative of patient populations that will benefit from a COVID-19 vaccine in clinical practice.

10.11.4.3. Justification for Dose

See Section 4.3 for a justification of the BNT162b2 and BNT162b2 OMI dose used in Substudy E.

10.11.4.4. End of Study Definition

See Section 4.4.

10.11.5. Study Population

Details of the master and Substudy E eligibility criteria are shown in Section 5. Participants must meet all of the general inclusion and exclusion criteria as specified for the master protocol as well as Substudy E–specific inclusion and exclusion criteria.

10.11.5.1. Inclusion Criteria

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

Age and Sex:

1. Groups 1 to 6: Male or female participants >55 years of age

   or

   Groups 7 to 9: Male or female participants 18 to 55 years of age

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

Type of Participant and Disease Characteristics:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.15.

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.

Other Inclusions:

5. Participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being 5 to 12 months (150 to 360 days) before Visit 601 (Day 1).

   Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

6. Groups 7 to 9 (sentinel participants): Screening troponin levels must be within normal range prior to randomization.

10.11.5.2. Exclusion Criteria

Participants are excluded from Substudy E 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. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

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

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

6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

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

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

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

10.11.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy E as detailed in Section 5.3 and Section 10.4.

10.11.5.4. Screen Failures

See Section 5.4.

10.11.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.11.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- Combination of BNT162b2 and BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg (site-prepared dosing suspension from 1 vial each of diluted BNT162b2 and BNT162b2 OMI for the sentinel-cohort participants in Groups 1 to 6, or a preformulated bivalent mixture [no dilution required] in a single vial for the expanded-enrollment participants in Groups 1 to 6 and for all cohorts in Groups 7 to 9).

Note: If the IRC's safety assessment is considered not to be acceptable, then the 60-µg dose levels for BNT162b2, BNT162b2 OMI, and the combination of BNT162b2 and BNT162b2 OMI may be replaced by 50-µg dose levels for the expanded enrollment (combination of BNT162b2 and BNT162b2 OMI at 25 µg each).

10.11.6.1. Study Intervention(s) Administered

Additional Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	Combination BNT162b2 and BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) Site-Prepared Dosing Suspension Using 2 Vials (Dilution Required)	Combination BNT162b2 Bivalent [Wild Type and Omicron (B.1.1.529)] Preformulated as a Single Vial (No Dilution Required)
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA	modRNA
Unit Dose Strength(s)	10 µg/0.1 mL	10 µg/0.1 mL	10 µg/0.1 mL	10 µg/0.1 mL
Dosage Level(s)	30-µg or 60-µg[a]	30-µg or 60-µg[a]	30-µg (15-µg each) or 60-µg (30-µg each)[a]	30-µg (15-µg each) or 60-µg (30-µg each)[a]
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor[b]	Provided centrally by the sponsor[c]

Additional Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	Combination BNT162b2 and BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) Site-Prepared Dosing Suspension Using 2 Vials (Dilution Required)	Combination BNT162b2 Bivalent [Wild Type and Omicron (B.1.1.529)] Preformulated as a Single Vial (No Dilution Required)
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

a. If the IRC's safety assessment is considered not to be acceptable, then the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
b. The combination of BNT162b2 and BNT162b2 OMI for the sentinel-cohort participants in Groups 1 to 6 will be a dosing suspension prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine at the dose levels shown in this table.
c. The bivalent formulation of BNT162b2 and BNT162b2 OMI for the expanded-cohort participants in Groups 1 to 6 and for all cohorts in Groups 7 to 9 will be provided as a preformulated suspension for injection in a single vial. No dilution is required.

10.11.6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 601 in accordance with the substudy's SoA (Section 10.11.1.3).

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

10.11.6.1.2. Preparation and Dispensing

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

10.11.6.2. Measures to Minimize Bias: Randomization and Blinding

10.11.6.2.1. Blinding of Site Personnel

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.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.11.6.2.2. Blinding of the Sponsor

The sponsor will be unblinded to the study intervention allocation for the sentinel cohorts. For the expanded-enrollment part of the study, the majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC and IRC (see Section 10.11.9.4.2). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

When a participant has completed their 3-month visit (Visit 604), they may be unblinded to confirm the vaccine and dose received. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.11.6.2.3. 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.

10.11.6.3. Study Intervention Compliance

See Section 6.4.

10.11.6.4. Dose Modification

See Section 6.5.

10.11.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.11.6.6. Treatment of Overdose

See Section 6.7.

10.11.6.7. Concomitant Therapy

See Section 6.8.

10.11.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.11.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 250 mL. Sentinel-cohort participants in Groups 7, 8, and 9 will also have 20 mL of blood drawn for troponin measurements. Those participants in the subset who consent to additional blood collection for isolation of PBMCs will have a total blood sampling volume of up to approximately 855 mL.

For all participants, 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.

10.11.8.1. Surveillance for COVID-19

If, at any time, a participant develops acute respiratory illness (see Section 10.11.8.6.8), for the purposes of the study, he or she will be considered to potentially have COVID-19 illness. In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid Xpert Xpress SARS-CoV-2; authorized by the FDA under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (ie, NAAT) to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 10.11.8.6.9) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

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

- Vomiting.

- Confirmed severe COVID-19 (FDA definition[45]): confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an ICU;
  - Death.

- Confirmed severe COVID-19 (CDC definition[46]): confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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

10.11.8.2. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The test to be performed will be the SARS-CoV-2 neutralizing assay (reference strain and Omicron strain). Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

Additional whole blood samples of ~120 mL will be obtained from a group of up to approximately 30 participants in each >55-year age group (Groups 1 to 6) and up to approximately 90 participants across the 18- to 55-year age groups (Groups 7 to 9) during the extended enrollment (no sentinel participants will have this additional blood sample drawn) for isolation of PBMCs. These samples will be used to describe B-cell and T-cell responses

to Omicron and the reference strain. A blood sample of ~5 mL for HLA typing will also be obtained.

10.11.8.3. Safety Assessments

See Section 8.2.

10.11.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.11.8.5. Specified Genetics

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

See Appendix 16 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

10.11.8.6. Substudy E Procedures

10.11.8.6.1. Screening (0 to 14 Days Before Visit 601) (Only for Sentinel-Cohort Participants 18 to 55 Years of Age in Groups 7, 8, and 9)

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 prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- 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.
- Collect a blood sample (approximately 10 mL) for troponin levels.
- 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 10.11.8.6.9.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

10.11.8.6.2. Visit 601 – Substudy E Vaccination (Day 1)

For Participants >55 Years of Age in Groups 1 to 6 and Expanded-Cohort Participants 18 to 55 Years of Age in Groups 7 to 9:

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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's prior study and participant number (if applicable) and record this in the CRF.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

For All Participants:

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation and a further blood sample (approximately 5 mL) for HLA typing.

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

- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.

- 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.

- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.2.4), 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 reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.11.8.6.8 for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.6.12).
- 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 10.11.8.6.9.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the reactogenicity 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.

10.11.8.6.3. Visit 601A – 3-Day Follow-Up Visit (2 to 4 Days After Visit 601) (Only for Sentinel-Cohort Participants 18 to 55 Years of Age in Groups 7, 8, and 9)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample (approximately 10 mL) for troponin levels (only for sentinel-cohort participants 18 to 55 years of age in Groups 7, 8, and 9).
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.6.12).
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.11.8.6.9.
- Ensure the participant has a self-swab kit.
- 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.
- 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.

10.11.8.6.4. Visit 602 – 1-Week Follow-Up Visit (6-8 Days After Visit 601)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.11.8.6.12).
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.11.8.6.9.
- Ensure the participant has a self-swab kit.

- 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.
- 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.

10.11.8.6.5. Visit 603 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 601)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.11.8.6.9.
- Ensure the participant has a self-swab kit.
- 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.

10.11.8.6.6. Visit 604 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 601)

- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.11.8.6.9.
- Ensure the participant has a self-swab kit.
- 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.

10.11.8.6.7. Visit 605 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 601)

- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity testing.
- If the participant is part of the group for description of cell-mediated immune response (select sites only), collect a blood sample (approximately 120 mL) for PBMC isolation.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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.

10.11.8.6.8. COVID-19 Surveillance (All Substudy E Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;

- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 10.11.8.6.10) 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.

10.11.8.6.9. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

  - Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);

    - Significant acute renal, hepatic, or neurologic dysfunction;

    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).

  - Clinical diagnosis.

  - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

  - Full blood count.

  - Blood chemistry, specifically creatinine, urea, LFTs, and C-reactive protein.

  - Imaging results (eg, CT or MRI scan) to document neurologic dysfunction.

  - Number and type of any healthcare contact; duration of hospitalization and ICU stay.

  - Death.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

10.11.8.6.10. 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 the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

10.11.8.6.11. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 601: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 601 swab, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.11.8.6.12. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis. In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

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

If a Grade 3 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 a suspected Grade 4 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 that 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 8.2.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.4.3.
- 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.

10.11.9. Statistical Considerations for Substudy E

See Section 9 for master protocol statistical considerations, and see substudy specifics below.

10.11.9.1. Statistical Hypotheses

10.11.9.1.1. Estimands

The estimands corresponding to the primary and exploratory objectives are described in the table in Section 10.11.3.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.11.9.1.2. Statistical Hypotheses

The primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated by the following statistical hypotheses. The immunogenicity objectives for participants 18 through 55 years are descriptive only.

Superiority and Noninferiority of Anti-Omicron Immune Responses

The primary immunogenicity objectives are to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti-Omicron immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age. Each primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(2) corresponds to a 1-fold superiority criterion and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 OMI or bivalent BNT162b2 and BNT162b2 OMI given as a fourth dose;

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose (Group 1).

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI or bivalent BNT162b2 and BNT162b2 OMI given as a fourth dose;

  - p_2 is the percentage of participants with seroresponse to the Omicron strain at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose (Group 1).

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Superiority will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

The secondary objective of "super" superiority will be evaluated using a 1.5-fold margin for GMR. "Super" superiority for GMR will be established if the lower limit of the 2-sided 95% CI for the GMR is greater than 1.5.

Noninferiority of Anti–Reference Strain Immune Responses

The noninferiority immunogenicity objectives on anti–reference strain immune responses are to assess the noninferiority of the anti–reference strain immune response induced by a dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti–reference strain immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age. Each noninferiority objective will be evaluated by the following hypotheis:

- The null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference strain–neutralizing titers measured 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose (Group 5 or Group 6);
  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference strain–neutralizing titers measured 1 month after 1 dose of BNT162b2 given as a fourth dose (Group 1).

Noninferiority based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

10.11.9.1.3. Multiplicity Adjustment

The primary and secondary immunogenicity objectives for participants >55 years of age will be assessed using the expanded-enrollment cohort.

The primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G4vG1A (OMI-60) → G6vG1A (bivalent-60) → G5vG1A (bivalent-30) →
- Noninferiority in GMR for reference strain response: G6vG1B (bivalent-60) → G5vG1B (bivalent-30) →
- "Super" superiority in GMR for Omicron response: G4vG1B (OMI-60) → G6vG1C (bivalent-60) → G5vG1C (bivalent-30) →
- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G3vG1A (OMI-30) → G3vG1B (OMI-30)

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference will be assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled.

The immunogenicity objectives for participants 18 through 55 years of age are descriptive only; therefore, no multiplicity adjustment is applied.

10.11.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

10.11.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and exploratory endpoints.

10.11.9.3.1. General Considerations

All analyses will be performed separately for each age group (18-55 years of age, >55 years of age).

Refer to Section 9.3.1 for general considerations of statistical analyses.

A sensitivity analysis of GMR and difference in seroresponse rate for between-group comparison may be performed. The GMR and associated 95% CI will be calculated by exponentiating the difference in least-squares means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of baseline assay results (log scale) and vaccine group. The difference in seroresponse rate between 2 vaccine groups and the associated 95% CI will be calculated using the stratified Miettinen and Nurminen method adjusting for the corresponding baseline assay result category (< median, ≥ median).

10.11.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Safety	For each age group (18-55 years of age, >55 years of age): • Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group. For sentinel-cohort participants 18 to 55 years of age: • Counts and percentages of participants with elevated troponin I levels before and 3 days after study vaccination, and associated Clopper-Pearson 95% CIs, will be provided for each vaccine group.
Immunogenicity	For each primary immunogenicity estimand described in Section 10.11.3, • GMRs and the associated 2-sided 95% CIs will be calculated using the method described in Section 9.3.1.2.3. • The percentages of participants with seroresponse for each group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (see Section 9.3.1.1). • Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis. • Superiority based on GMR will be established if the lower bound of the 2-sided 95% CI for the GMR is >1. Noninferiority based on seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than -5%. • GMRs and the associated 2-sided 95% CI, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs, may be estimated using the sensitivity analysis approach specified in Section 10.11.9.3.1.

10.11.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	For each secondary immunogenicity estimand described in Section 10.11.3. • GMR and the associated 2-sided 95% CIs will be calculated using the same method as for the primary immunogenicity objectives. • Noninferiority of anti–reference strain immune response based on the GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8. • "Super" superiority of anti-Omicron immune response will be established if the lower bound of the 2-sided 95% CI for the GMR is >1.5. • GMRs and the associated 2-sided 95% CI may be estimated using the sensitivity analysis approach specified in Section 10.11.9.3.1.

10.11.9.3.4. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMTs and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers** **Percentages of participants with seroresponse to Omicron- or reference-strain** For each age group (18-55 years of age, >55 years of age): • GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. • The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. • GMRs and the differences in percentages of participants with seroresponse between certain vaccine groups of interest may be calculated along with the associated 2-sided 95% CIs.

Endpoint	Statistical Analysis Methods
	GMTs and GMFRs of SARS-CoV-2 reference-strain and VOC-neutralizing titers for participants in the sentinel cohorts For each age group (18-55 years of age, >55 years of age): • GMTs at each time point and GMFRs of SARS-CoV-2 reference-strain and VOC-neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group for sentinel cohorts. **GMTs for any VOCs not already specified** For each age group (18-55 years of age, >55 years of age): • GMTs of reference-strain or VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs and GMRs of VOC-neutralizing titers to reference-strain–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized for each age group.
Cell-mediated immune response	The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron will be summarized at each time point for the subset of participants with PBMC samples collected in each vaccine group for each age group.

10.11.9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

10.11.9.4.1. Analysis Timing

Statistical analyses will be carried out when the following data are available for each age group:

- Safety data through 1 month after study vaccination for each group in the sentinel cohorts.

- Immunogenicity data through 1 month after study vaccination for each group in the sentinel cohorts.
- Safety data through 1 month after study vaccination for each group in the expanded-enrollment cohort.
- Immunogenicity data through 1 month after study vaccination for each group in the expanded-enrollment cohort.
- Complete safety and immunogenicity analysis approximately 6 months after study vaccination for each group in the sentinel or expanded-enrollment cohorts.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses for the expanded-enrollment cohort conducted while the study is ongoing will be performed by an unblinded team.

10.11.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

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

The responsibilities of the IRC are only for the sentinel cohort and will include:

- Review of all reported AEs, e-diary reactogenicity data, and troponin levels collected through Day 7 from all sentinel-cohort participants. This safety assessment will be conducted to determine if the study team may proceed with expanded enrollment of approximately 300 participants per group.

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

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

10.11.9.5. Sample Size Determination

The sample size in each group is based on consideration of an acceptable safety database. For the >55-year age group, a random sample of 230 participants will be selected from each group in the expanded-enrollment cohort as an immunogenicity subset to evaluate the primary and secondary immunogenicity objectives. Assuming a 35% nonevaluable or prior infection rate, approximately 150 evaluable participants in each group will contribute to the primary immunogenicity evaluation. –

Superiority and Noninferiority of Anti-Omicron Immunogenicity Objectives

For comparisons based on GMR, assuming common assay standard deviations of 1.05 in log scale based on data observed in the Phase 2 part of the C4591001 study for participants 56 years of age or older and adjusted for assay variability, if the true GMR is 1.5, with 150 evaluable participants, the study will have 91.5% power to demonstrate superiority. If the true GMR is 2.0, the study will have 65.7% power to declare “super” superiority using a 1.5-fold margin.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 70% in the BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) group and 55% in the BNT162b2 30 µg group, the study will have 94.9% power to demonstrate noninferiority using a 5% margin.

Noninferiority of Anti–Reference Strain Immunogenicity Objectives

For comparisons based on GMR, common assay standard deviations of 1.05 and a GMR of 1 are assumed for each comparison. With 150 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has 90.9% power to demonstrate noninferiority based on the GMR using a 1.5-fold margin.

For safety outcomes, Table 15 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 1%, with 300 participants in a vaccine group, there is 95% probability of observing at least 1 AE.

Table 15. Substudy E – Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=20	N=300	N=900	N=1920
0.01%	0.002	0.03	0.09	0.17
0.02%	0.004	0.06	0.16	0.32
0.05%	0.01	0.14	0.36	0.62
0.10%	0.02	0.26	0.59	0.85
0.20%	0.04	0.45	0.84	0.98
0.50%	0.10	0.78	0.99	>0.99
1.00%	0.18	0.95	>0.99	>0.99
2.00%	0.33	>0.99	>0.99	>0.99
5.00%	0.64	>0.99	>0.99	>0.99
10.0%	0.88	>0.99	>0.99	>0.99

10.12. Appendix 12: Substudy F

10.12.1. Substudy Summary

10.12.1.1. Substudy Synopsis

See Section 1.1 for a synopsis of Substudy F.

10.12.1.2. Schema

Visit Number	701	702	703	704	705
Visit Description	4th Dose of BNT162b2 or BNT162b2 OMI or Combination BNT162b2/BNT162b2 OMI	7 Days After 4th Vaccination	1 Month After 4th Vaccination	3 Months After 4th Vaccination	6 Months After 4th Vaccination
Participants having received 3 prior doses of 30 µg BNT162b2 ≥4 months prior to randomization	30-µg OR 60-µg dose				
Blood draw for immunogenicity assessments[a]	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL
Blood draw for additional laboratory testing[b]	~35 mL	~35 mL	~35 mL	~35 mL	~35 mL

a. ~11 mL for Pfizer central laboratory testing, ~11 mL for Sheba laboratory testing, and ~3 mL for BioNTech laboratory testing. See Section 10.12.8.2.
b. ~35 mL collected for PBMC for Sheba and BioNTech as described in Section 10.12.8.2.

10.12.1.3. Schedule of Activities for Substudy F

Visit Number	701	702	703	704	705	Unplanned
Visit Description	Vaccination	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit[a]
Visit Window (Days)	Day 1[b]	6 to 8 Days After Visit 701	28 to 35 Days After Visit 701	85 to 95 Days After Visit 701	175 to 189 Days After Visit 701	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Obtain informed consent	X					
Perform SARS-CoV-2 antigen test	X					
Assign participant number	X					
Obtain demography and medical history data	X					
Perform clinical assessment[c]	X					
Measure height and weight	X					
Measure temperature (body)	X					
Perform urine pregnancy test (if appropriate)	X					
Confirm use of contraceptives (if appropriate)	X	X	X			
Collect nonstudy vaccine information	X	X	X	X	X	
Collect prohibited medication use		X	X	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	
Confirm eligibility	X					
Review temporary delay criteria	X					
Collect blood sample for immunogenicity assessments[d]	~25 mL	~25 mL	~25 mL	~25 mL	~25 mL	
Collect blood sample for additional laboratory testing[e]	~35 mL	~35 mL	~35 mL	~35 mL	~35 mL	
Obtain nasal (midturbinate) swab	X					X
Obtain the participant's vaccine vial allocation using the IRT system	X					
Administer study intervention	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X					

Visit Number	701	702	703	704	705	Unplanned
Visit Description	Vaccination	1-Week Follow-Up Visit After Vaccination	1-Month Follow-Up Visit After Vaccination	3-Month Follow-Up Visit After Vaccination	6-Month Follow-Up Visit After Vaccination	Potential COVID-19 Illness Visit[a]
Visit Window (Days)	Day 1[b]	6 to 8 Days After Visit 701	28 to 35 Days After Visit 701	85 to 95 Days After Visit 701	175 to 189 Days After Visit 701	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X					
Provide/ensure the participant has a thermometer and measuring device	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	X→	X→				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X			
Collect AEs and SAEs as appropriate	X	X	X[f]	X[f]	X[f]	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
Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs	X	X	X	X		

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

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. ~11 mL for Pfizer central laboratory testing, ~11 mL for Sheba laboratory testing, and ~3 mL for BioNTech laboratory testing. See Section 10.12.8.2.
e. ~35 mL collected for PBMC for Sheba and BioNTech as described in Section 10.12.8.2.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

10.12.2. Introduction

10.12.2.1. Study Rationale

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, is currently the dominant variant in many countries and within the US is responsible for 98.3% of sequenced COVID-19 cases as of 08 January 2022.[25] Current data note that the vaccine effectiveness against hospitalization is 88% (78%-93%) for Omicron after 3 doses of vaccine.[26] However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant. The addition of a higher-dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile.[27] Therefore, Substudy F has been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

See Section 2.2 for the study background.

10.12.2.2. Benefit/Risk Assessment

A tolerability profile of a 60-µg dose of BNT162b2 has yet to be established. However, BNT162b1 (a candidate RNA-LNP vaccine tested in clinical trial C4591001 utilizing nucleoside-modified messenger RNA similar to BNT162b2 but instead of encoding the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein, BNT162b1 encodes the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain) was studied in adults 18 to 55 years of age at dose levels of 50 µg, 60 µg, and 100 µg. In one study, 60 participants were vaccinated with BNT162b1. Twelve participants for each of the dose level groups (1 µg, 10 µg, 30 µg, 50 µg, and 60 µg) were to receive the first dose on Day 1 and a second dose on Day 22. Due to the tolerability observed in participants after 2 doses of 50 µg and after reviewing the totality of the data available, including the local and systemic reactogenicity data, such as the increasing number of severe (Grade 3) systemic reactions reported with ascending dose, a second dose of 60 µg was not administered.[37,47] Another study investigated BNT162b1 at 10 µg, 30 µg, and 100 µg. Participants in this study were not administered the second dose of 100 µg because of the increased reactogenicity profile seen after a single dose at 100 µg and in participants who received 2 doses of 30 µg.[38] In light of better tolerability of BNT162b2 (compared to BNT162b1), and better tolerability in older adults (compared to younger adults), the potential benefit of a 60-µg dose of BNT162b2 is likely to outweigh the risk.

10.12.2.2.1. Benefit Assessment

Benefits to individual participants enrolled in Substudy F may be:

- Receipt of a fourth dose of an efficacious or potentially efficacious COVID-19 vaccine that may convey a longer duration of protection during a global pandemic, particularly against new variant-associated infection and disease.

- Contributing to research to help others in a time of global pandemic.

10.12.3. Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
• To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a combination of BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• 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
Primary Immunogenicity		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a combination of BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose in BNT162b2-experienced participants	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponse[a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers SARS-CoV-2 reference-strain–neutralizing titers
• **Exploratory**		
To describe the immune response to any VOCs not already specified		• SARS-CoV-2 neutralizing titers for any VOCs not already specified
To describe the cell-mediated immune response and additional immune response parameters		• T-cell (by ELISPOT) and B-cell repertoire • Pseudo and micro neutralizing antibody titers • IgG • IgA
To describe confirmed COVID-19 and severe COVID-19 cases		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases

a. Seroresponse is defined as achieving ≥4 × LLOQ.

10.12.4. Study Design

10.12.4.1. Overall Design

This is a randomized, observer-blinded substudy to describe the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose. Approximately 180 participants ≥60 years of age who have received 3 prior

doses of BNT162b2 (30 µg doses) with the most recent dose being ≥4 months prior to randomization, will be enrolled in Israel. Participants will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 701 as a fourth dose.

Initially, sentinel cohorts (sponsor open-label) of 5 participants per group will be enrolled. An IRC and site representatives will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 25 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

Table 16 describes the enrollment of the sentinel cohorts and steps to progress to expanded enrollment.

Table 16. Substudy F – Sentinel and Expanded Enrollment

Sentinel Enrollment[a]	
Study Intervention	**Number of Participants**
BNT162b2 30 µg	5
BNT162b2 60 µg	5
BNT162b2 OMI 30 µg	5
BNT162b2 OMI 60 µg	5
Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)	5
Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)	5
IRC and site representatives' review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.	
Expanded Enrollment[b]	
Study Intervention	**Number of Participants**
BNT162b2 30 µg	25
BNT162b2 60 µg	25
BNT162b2 OMI 30 µg	25
BNT162b2 OMI 60 µg	25
Combination of BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)	25
Combination of BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)	25

a. Sentinel cohorts will be sponsor open-label.
b. If the IRC and site representative's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

10.12.4.2. Scientific Rationale for Substudy F Design

See Section 10.12.2.1.

10.12.4.3. Justification for Dose

See Section 4.3 for a justification of the BNT162b2 and BNT162b2 OMI dose used in Substudy F.

10.12.4.4. End of Study Definition

See Section 4.4.

10.12.5. Study Population

Details of the master eligibility criteria are shown in Section 5. Substudy F–specific eligibility criteria are listed in Sections 10.12.5.1 and 10.12.5.2.

10.12.5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥60 years of age:

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

Type of Participant and Disease Characteristics:

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

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

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.15.

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.

Other Inclusions:

5. Participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being ≥4 months before Visit 701 (Day 1).

Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

10.12.5.2. Exclusion Criteria

Participants are excluded from Substudy F 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. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

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

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

6. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

7. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

9. Prior receipt of any COVID-19 vaccine other than BNT162b2.

Other Exclusions:

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

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

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

10.12.5.3. Lifestyle Considerations

Contraception requirements will apply to Substudy F as detailed in Section 5.3 and Section 10.4.

10.12.5.4. Screen Failures

See Section 5.4.

10.12.5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

See Section 5.5.

10.12.6. Study Intervention(s) and Concomitant Therapy

For the purposes of this substudy, study intervention refers to:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.
- Combination of BNT162b2 and BNT162b2 OMI (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 30 µg or 60 µg.

Note: If the IRC and site representative's safety assessment is considered not to be acceptable, then the 60-µg dose levels for BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI may be replaced by 50-µg dose levels for the expanded enrollment (combination of BNT162b2 and BNT162b2 OMI at 25 µg each).

10.12.6.1. Study Intervention(s) Administered

Additional Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) (Dilution Required)	Combination BNT162b2 and BNT162b2 OMI (B.1.1.529) (BNT162 RNA-LNP Vaccine Utilizing modRNA) Site-Prepared Dosing Suspension Using 2 Vials (Dilution Required)
Type	Vaccine	Vaccine	Vaccine
Dose Formulation	modRNA	modRNA	modRNA
Unit Dose Strength(s)	10 µg/0.1 mL	10 µg/0.1 mL	10 µg/0.1 mL
Dosage Level(s)	30-µg or 60-µg[a]	30-µg or 60-µg[a]	30-µg (15-µg each) or 60-µg (30-µg each)[a]
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor[b]
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement

a. If the IRC's safety assessment is considered not to be acceptable, then the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
b. The combination of BNT162b2 and BNT162b2 OMI will be dosing suspension prepared at the investigator site from 1 vial each of diluted BNT162b2 Vaccine and BNT162b2 OMICRON (B.1.1.529) at the dose levels shown in this table.

10.12.6.1.1. Administration

Participants will receive 1 dose of study intervention as allocated by the IRT at Visit 701 in accordance with the substudy's SoA (Section 10.12.1.3).

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

10.12.6.1.2. Preparation and Dispensing

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

10.12.6.2. Measures to Minimize Bias: Randomization and Blinding

10.12.6.2.1. Blinding of Site Personnel

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. However, site personnel, separate from the site study team, that will review safety data with the IRC will be unblinded to the study intervention allocation for the sentinel cohort.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

10.12.6.2.2. Blinding of the Sponsor

The sponsor will be unblinded to the study intervention allocation for the sentinel cohort. For the expanded-enrollment part of the study the majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor/Pfizer staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC and IRC (see Section 10.12.9.4.2). This team comprises a statistician, programmer(s), a clinical scientist, and a medical monitor.

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of the statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study after the first planned analysis.

When a participant has completed their 3-month visit (Visit 704), they may be unblinded to confirm the vaccine and dose received. The study team will also become unblinded to the participant's original study intervention allocation at this time.

10.12.6.2.3. 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.

10.12.6.3. Study Intervention Compliance

See Section 6.4.

10.12.6.4. Dose Modification

See Section 6.5.

10.12.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

10.12.6.6. Treatment of Overdose

See Section 6.7.

10.12.6.7. Concomitant Therapy

See Section 6.8.

10.12.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7.

10.12.8. Study Assessments and Procedures

The total blood sampling volume for individual participants in this study is up to approximately 300 mL. For all participants, 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.

10.12.8.1. Surveillance for COVID-19

If, at any time, a participant develops acute respiratory illness (see Section 10.12.8.5.6), for the purposes of the study he or she will be considered to potentially have COVID-19 illness. In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid Xpert Xpress SARS-CoV-2; authorized by the FDA under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (ie, NAAT) to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 10.12.8.5.7) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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

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

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

- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

- Confirmed severe COVID-19 (FDA definition[45]): confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an ICU;
  - Death.
- Confirmed severe COVID-19 (CDC definition[46]): confirmed COVID-19 and presence of at least 1 of the following:
  - Hospitalization;
  - Admission to the ICU;
  - Intubation or mechanical ventilation;
  - Death.

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

10.12.8.2. Immunogenicity

Blood samples (~11 mL for Pfizer, ~11 mL for Sheba, and ~3 mL for BioNTech) for serum collection will be obtained for immunogenicity testing at each visit as specified in the SoA. The tests to be performed will be the SARS-CoV-2 neutralizing assays (reference strain and Omicron strain).

Additional whole blood samples (~20 mL for Sheba and ~15 mL for BioNTech) will be collected for PBMC isolation at each visit as specified in the SoA. The testing priority will be ~5 mL for T-cell analysis for Sheba, ~15 mL for B-cell analysis for BioNTech, and ~15 mL for B-cell analysis for Sheba. PBMC analysis will include T-cell by ELISPOT and B-cell repertoire, which is currently being developed. IgG and IgA will also be tested and for a subset of participants will be assessed for avidity.

10.12.8.3. Safety Assessments

See Section 8.2.

10.12.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

10.12.8.5. Substudy F Procedures

10.12.8.5.1. Visit 701 – Substudy F Vaccination (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. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Perform a SARS-CoV-2 antigen test and confirm that the participant is negative. Record the result in the source documents only.
- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record the HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record any findings on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Blinded site staff will obtain the participant's randomization number using the IRT system. The randomization confirmation report with the study intervention allocation will only be sent to the unblinded site staff member.
- 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.
- Provide a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and fever (COVID-19 surveillance) and provide instructions on their use.

- Explain the e-diary technologies available for this study (see Section 8.2.4), 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 reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See Section 10.12.8.5.6 for further details. Provide a self-swab kit in case of COVID-19 symptoms and provide instructions on self-collection of nasal swabs.

- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through 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 the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.12.8.5.10).

- 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 10.12.8.5.7.

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

- Remind the participant to bring the reactogenicity 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.

10.12.8.5.2. Visit 702 – 1-Week Follow-Up Visit (6-8 Days After Visit 701)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.12.8.5.10).
- 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 the participant experiences any respiratory symptoms as detailed in Section 10.12.8.5.7.
- Ensure the participant has a self-swab kit.
- 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.
- 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.

10.12.8.5.3. Visit 703 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 701)

- 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 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- Discuss contraceptive use as described in Section 5.3.
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory 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 the participant experiences any respiratory symptoms as detailed in Section 10.12.8.5.7.
- Ensure the participant has a self-swab kit.
- 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.

10.12.8.5.4. Visit 704 – 3-Month Follow-Up Visit (85 to 95 Days After Visit 701)

- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Record nonstudy vaccinations as described in Section 6.8.

- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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 10.12.8.5.7.
- Ensure the participant has a self-swab kit.
- 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.

10.12.8.5.5. Visit 705 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 701)

- Record AEs as described in Section 8.3.
- Collect a blood sample for immunogenicity assessments.
- Collect a whole blood sample for additional laboratory testing.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record the latest CD4 count and HIV viral load.
- 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.

10.12.8.5.6. COVID-19 Surveillance (All Substudy F Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs.

Participants may utilize a COVID-19 illness e-diary through an application (see Section 10.12.8.5.8) 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.

10.12.8.5.7. Potential COVID-19 Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.8 received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if the visit is conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
    - Symptoms and signs, including
        - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
        - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
        - Significant acute renal, hepatic, or neurologic dysfunction;
        - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).

- Clinical diagnosis.
- Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.
- Full blood count.
- Blood chemistry, specifically creatinine, urea, LFTs, and C-reactive protein.
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction.
- Number and type of any healthcare contact; duration of hospitalization and ICU stay.
- Death.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.12.8.5.8. 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 the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- If a participant is not actively completing the COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

10.12.8.5.9. SARS-CoV-2 NAAT Results

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 701: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 701 swab, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

10.12.8.5.10. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis. In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

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

If a Grade 3 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever (Section 8.2.4.4) 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 a suspected Grade 4 local reaction (Section 8.2.4.2), systemic event (Section 8.2.4.3), or fever

(Section 8.2.4.4) 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 that 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 8.2.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.4.3.
- 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.

10.12.9. Statistical Considerations for Substudy F

See Section 9 for master protocol statistical considerations, and see substudy specifics below.

10.12.9.1. Statistical Hypotheses

10.12.9.1.1. Estimands

The estimands corresponding to the primary and exploratory objectives are described in the table in Section 10.12.3.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

10.12.9.1.2. Statistical Hypotheses

All objectives in this substudy are descriptive. No hypothesis testing is planned.

10.12.9.1.3. Multiplicity Adjustment

No multiplicity adjustment is needed for the study as there is no statistical hypothesis.

10.12.9.2. Analysis Sets

For the purpose of analysis, the following analysis sets are defined for this substudy:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

10.12.9.3. Statistical Analyses

The SAP will be developed and finalized for this substudy before any analyses are performed and will describe the analyses and procedures for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.12.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of statistical analyses.

10.12.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after the study vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. • AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs within 1 month and SAEs within 6 months after study vaccination will be provided for each vaccine group.
Immunogenicity	**GMTs and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers** **Percentages of participants with seroresponse to Omicron- or reference-strain** • GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group using the statistical method described in Section 9.3.1.2.1 and Section 9.3.1.2.2. • The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

10.12.9.3.3. Exploratory Endpoint(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMTs for any VOCs not already specified** GMTs of reference-strain or VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs and GMRs of VOC-neutralizing titers to reference-strain–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs. **Cell-mediated immune response and additional immune response parameters** The cell-mediated immune response and additional immune response parameters will be summarized at each time point.
COVID-19 cases	Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.

10.12.9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

10.12.9.4.1. Analysis Timing

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

- Safety data through 1 month after study vaccination for each group.
- Immunogenicity data through 1 month after study vaccination for each group.
- Complete safety and immunogenicity analysis approximately 6 months after study vaccination for each group.

Certain analyses may be combined into a single regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses for the expanded-enrollment cohort conducted while the study is ongoing will be performed by an unblinded team.

10.12.9.4.2. Data Monitoring Committee or Other Independent Oversight Committee

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

The responsibilities of the IRC and site representatives are only for the sentinel cohort and will include:

- Review of all reported AE and e-diary reactogenicity data collected through Day 7 from all sentinel-cohort participants. This safety assessment will be conducted to determine if the study team may proceed with expanded enrollment of approximately 25 additional participants per group.

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

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

10.12.9.5. Sample Size Determination

The study size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

Table 17 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 1%, with 30 participants in a vaccine group, there is 26% probability of observing at least 1 AE.

Table 17. Substudy F - Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=30	N=90	N=180
0.01%	0.003	0.01	0.02
0.02%	0.006	0.02	0.04
0.05%	0.01	0.04	0.09
0.10%	0.03	0.09	0.16
0.20%	0.06	0.16	0.30
0.50%	0.14	0.36	0.59
1.00%	0.26	0.60	0.84
2.00%	0.45	0.84	0.97
5.00%	0.79	0.99	>0.99
10.0%	0.96	>0.99	>0.99

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 9 (03 May 2022)

Overall Rationale for the Amendment:

The inclusion criteria for Substudy B have been updated to allow participants who have received a third dose of BNT162b2 at least 4 months prior to randomization, to support enrollment and to align with current recommendations.

Substudy E has been amended to obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recomendations.
Section 1.1 – Synopsis, Substudy E	Added sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E and updated the number of participants to 2910 for Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.8.1.2 – Schema for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.1.3 – SoA for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.

Section # and Name	Description of Change	Brief Rationale
Section 10.8.2.1 – Study Rationale for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.4.1 – Overall Design for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.5.1 – Inclusion Criteria for Substudy B	Updated criteria to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.8.8.3.1 – Visit 201 for Substudy B	Added text to allow inclusion of participants who have received a booster (third) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior BNT162b2 for participants with 2 prior doses updated to 4 months prior to randomization.	To support enrollment and to align with current recommendations.
Section 10.10.8.6.2.3 – Visit 404 for Substudy D	Moved the following text and changed it from a procedure to a note: Participants in Cohort 2 will be unblinded to confirm the vaccine received once they have **COMPLETED** Visit 404 (3 months after Substudy D Vaccination 1). Since these are the only participants still blinded at this time, the study team will also become unblinded to all participants' original study intervention allocation at this time.	To prevent sites from unblinding participants prematurely.
Section 10.11.1.2 – Schema for Substudy E	Added sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.1.3 – SoA for Substudy E	Added sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.3 – Objectives, Estimands, and Endpoints for Substudy E	Updated the primary and secondary objectives with respect to noninferiority of the seroresponse rate and updated the definition of seroresponse and added text and objectives for the 18- to 55-year-olds.	To align with regulatory requirements and to describe the analysis of data from 18- to 55-year-olds.
Section 10.11.4 – Overall Design for Substudy E	Added text to include sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.5.1 – Inclusion Criteria for Substudy E	Updated inclusion criterion 1 for sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E. Added a new exclusion criterion for sentinel participants in Groups 7 to 9 requiring that screening troponin levels must be within normal range prior to randomization.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.6 – Study Intervention(s) and Concomitant Therapy for Substudy E	Added text to include sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.8 – Study Assessments and Procedures for Substudy E	Added text to specify that sentinel cohort participants in Groups 7, 8, and 9 will also have 20 mL of blood drawn for troponin levels.	Troponin levels will be obtained at screening and on Day 3.
Section 10.11.8.2 – Immunogenicity for Substudy E	Added text to specify that up to approximately 90 participants across the 18- to 55-year-old groups (Groups 7 to 9) will contribute to PBMC sample collection.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.8.6 – Substudy E Procedures	Added text to include sentinel and expanded cohorts of participants 18 to 55 years of age in Substudy E.	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in 18- to 55-year-olds.
Section 10.11.9 – Statistical Considerations for Substudy E	Updated hypotheses, multiplicity, analysis, and sample size calculation related to changes in objectives and added text and objectives for the 18- to 55-year-olds.	To align with regulatory requirements and to describe the analysis of data from 18- to 55-year-olds.

Amendment 8 (31 Mar 2022)

Overall Rationale for the Amendment:

Added language to permit early discontinuation of participants in Substudy A for reasons including (but not limited to) access and availability of BNT162b2 in the real world, reducing the need for participant involvement and observation in this clinical trial.

Substudy B was updated to clarify that participants may be unblinded to confirm the dose of BNT162b2 received at Visit 205, 1 month after receiving their second study vaccination. This amendment will allow for collection of data after a dose of BNT162b2 OMI at Visit 404 in Substudy D Group 3 and Group 4 participants who received 3 prior doses of BNT162b2 and a fourth dose of either BNT162b2 or BNT162b2 OMI. Substudy D updates also include changes to the statistical considerations to align with CBER feedback.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Rationale	Updated text to state that to date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died.	To provide the most current information.
Section 1.1 – Synopsis, Substudy A Design	Added language to permit early discontinuation of participants in Substudy A.	Due to access and availability of BNT162b2 in the real world, and for participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Substudy D Design	Added text for Cohort 2 to clarify that participants will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Removed text stating that Group 4 may not be enrolled.	To allow for collection of data after a dose of BNT162b2 OMI at Visit 404 in participants who received 3 prior doses of BNT162b2 and a fourth dose of either BNT162b2 or BNT162b2 OMI. Group 4 was enrolled.
Section 2.2 – Background	Updated text to state that to date, more than 455 million people have been infected with SARS-CoV-2 and >6 million have died.	To provide the most current information.
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information, Substudy D	Added text to clarify the AE collection time period for Group 3 and Group 4 participants who will receive a dose of BNT162b2 OMI at Visit 404.	To account for a dose of BNT162b2 OMI administered to Group 3 and Group 4 participants at Visit 404.
Section 10.7.4 – Study Design for Substudy A	Added language to permit early discontinuation of participants in Substudy A.	Due to access and availability of BNT162b2 in the real world, and for participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program.
Section 10.8.6.2.2 – Blinding of the Sponsor for Substudy B	Added text to clarify that the participant may be unblinded to confirm the dose of BNT162b2 received at Visit 205, 1 month after receiving their second study vaccination. The study team will also become unblinded to the participant's original study intervention allocation at this time.	To allow participants to add the vaccination details to their national vaccination record cards.
Section 10.8.8.3.3 - Visit 203 – Vaccination 2 (28 to 35 Days After Visit 201) for Substudy B	Addition of the step to measure the participant's body temperature.	Protocol clarification.
Section 10.9.8.4.3 Visit 303 – 1 Month After Booster Vaccination (28 to 35 Days After Visit 301) for Substudy C	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.9.3 – Objectives, Estimands, and Endpoints for Substudy C	Corrected the age group ranges in the second primary immunogenicity objective: 18 through 30 years of age and 31 through 55 years of age.	To correct a typographical error in the previous version.
Section 10.9.9.3.4 – Exploratory Endpoint(s) Analysis for Substudy C	Removed "anti" from anti-VOC neutralizing titers, as the term "anti" in this context is extraneous.	To correct a typographical error in the previous version.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.1.2.1 – Schema for Substudy D	Added a row to confirm the participant's prior study and participant number (if applicable) should be recorded in the CRF.	Protocol clarification.
Section 10.10.1.2.2 – Schema for Substudy D	Added a separate schema for Cohort 2 participants.	To account for the second dose of BNT162b2 OMI administered to Group 3 and 4 participants.
Section 10.10.1.3 – Schedule of Activities for Substudy D	Added a separate schedule of activities for Cohort 2 participants.	To account for the second dose of BNT162b2 OMI administered to Group 3 and 4 participants.
Section 10.10.3 – Objectives, Estimands, and Endpoints for Substudy D	Updated the primary and secondary objectives with respect to noninferiority of the seroresponse rate and updated the definition of seroresponse.	To align with regulatory requirements.
Section 10.10.4.1 – Study Design for Substudy D	Added text for Cohort 2 participants to clarify that they will be offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Removed text stating that Group 4 may not be enrolled.	To allow for collection of data after a dose of BNT162b2 OMI at Visit 404 in participants who received 3 prior doses of BNT162b2 and either a fourth dose of BNT162b2 or BNT162b2 OMI. Group 4 was enrolled.
Section 10.10.6.1.1 – Administration for Substudy D	Added text to indicate that Group 3 and Group 4 participants may receive a dose of BNT162b2 OMI at Visit 404.	To account for a dose of BNT162b2 OMI administered to Group 3 and Group 4 participants at Visit 404.
Section 10.10.6.2.1 – Blinding of the Site Personnel for Substudy D	Added text to allow Cohort 2 to be unblinded at Visit 404.	To allow participants to add the vaccination details to their national vaccination record cards.
Section 10.10.6.2.2 – Blinding of the Sponsor for Substudy D	Added text to allow Cohort 2 to be unblinded at Visit 404.	To allow participants to add the vaccination details to their national vaccination record cards.
Section 10.10.8.6 – Substudy D Procedures	Added a subsection of procedures for Cohort 2.	To account for a dose of BNT162b2 OMI administered to Group 3 and Group 4 participants.
Section 10.10.8.6.1.2 Visit 402 – 1-Month Follow-Up Visit (After Substudy D Vaccination 1) (28 to 35 Days After Visit 401) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.10.8.6.1.3 Visit 403 – 1-Month Follow-Up Visit (After Substudy D Vaccination 2) (28 to 35 Days After Visit 402) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.8.6.3.4 Visit 504 – 1-Month Follow-Up Visit (After Vaccination 2) (28 to 35 Days After Visit 502) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.10.8.6.3.7 Visit 507 – 1-Month Follow-Up Visit (After Vaccination 3) (28 to 35 Days After Visit 506) for Substudy D	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.10.8.6.6 – SARS-CoV-2 NAAT Results for Substudy D	Added Visit 404 (Group 3 and Group 4 participants who receive a dose of BNT162b2 OMI at Visit 404) to the list of nasal swab visit time points that will be used to determine whether a participant will be included in the immunogenicity analysis. Clarified the analysis (immunogenicity) and time points of those with no serological or virological evidence (up to 1 month after receipt of the third, fourth, or fifth dose for BNT162b2-experienced participants, or as a 2-dose series to COVID-19 vaccine–naïve participants) of past SARS-CoV-2 infection.	To account for the dose of BNT162b2 OMI administered to Group 3 and Group 4 participants at Visit 404. To correct the analysis population and time points of past SARS-CoV-2 infection.
Section 10.10.9 – Statistical Considerations for Substudy D	Updated hypotheses, multiplicity, analysis, and sample size calculation related to changes in objectives.	To align with regulatory requirements.
Section 10.10.9.3.4 – Exploratory Endpoint(s) Analysis for Substudy D	Removed “anti” from anti-VOC neutralizing titers, as the term “anti” in this context is extraneous.	To correct a typographical error in the previous version.
Section 10.11.4.1 – Overall Design for Substudy E	Added group number to the Sentinel and Expanded Enrollment table.	To provide more clarity when referring to groups in the Statistical Considerations section.
Section 10.11.8.6.5 Visit 603 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 601) for Substudy E	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.11.9.3.4 – Exploratory Endpoint(s) Analysis for Substudy E	Removed “anti” from anti-VOC neutralizing titers, as the term “anti” in this context is extraneous.	To correct a typographical error in the previous version.

Section # and Name	Description of Change	Brief Rationale
Section 10.12.8.5.3 Visit 703 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 701) for Substudy F	Deleted the request to ask the participant or his/her parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	Protocol clarification as outside of the reporting period.
Section 10.12.9.3.3 – Exploratory Endpoint(s) Analysis for Substudy F	Removed "anti" from anti-VOC neutralizing titers as the term "anti" in this context is extraneous.	To correct a typographical error in the previous version.
Section 10.12.9.4.1 – Analysis Timing for Substudy F	Removed the analysis for immunogenicity data through 7 days after study vaccination for each group and safety data through 7 days after study vaccination for each group.	Data from Substudy E will be used to inform decisions at this immunogenicity time point. Safety data at 7 days after study vaccination are covered by the IRC review.

Amendment 7 (17 Feb 2022)

Overall Rationale for the Amendment:

A BNT162b2 bivalent (BNT162b2 Wild Type and BNT162b2 OMI) formulation will be available as a preformulated product in Substudy E. The sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will be administered a suspension containing a mixture of BNT162b2 Wild Type and BNT162b2 OMI prepared from 2 separate vials at the investigator site. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the preformulated product containing BNT162b2 Wild Type and BNT162b2 OMI.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 10.10.9.3.2 – Primary Endpoint(s)/Estimand(s) Analysis for Substudy D	Updated text to clarify that superiority based on GMR will be established if the lower bound of the 2-sided 97.5% CI for the GMR is >1.	To correct a typographical error in the previous version.
Section 10.10.6.2 – Measures to Minimize Bias: Randomization and Blinding for Substudy D	Removed "(Cohort 2 Only)" from the header as the text included in the subsections referenced Cohort 1 as well.	To clarify that the section contains text for Cohort 1.
Section 10.9.6.2.2 – Blinding of the Sponsor for Substudy D	Added text to clarify sponsor blinding to Cohort 1, Groups 1 and 2b, as specified elsewhere within this subsection.	To clarify and reiterate sponsor blinding to Cohort 1, Groups 1 and 2b.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.4 – Study Design for Substudy E	Updated footnotes to clarify that the sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive doses that are prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required	To study a preformulated BNT162b2 bivalent mixture of BNT162b2 Wild Type and BNT162b2 OMI.
Section 10.11.6 – Study Intervention(s) and Concomitant Therapy for Substudy E	Updated text to clarify that the sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will be administered a suspension containing a mixture of BNT162b2 Wild Type and BNT162b2 OMI prepared from 2 separate diluted vials at the investigator site. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the preformulated bivalent mixture from a single vial (no dilution required).	To study a preformulated BNT162b2 bivalent mixture of BNT162b2 Wild Type and BNT162b2 OMI.
Section 10.11.6.1 – Study Intervention(s) Administered for Substudy E	Added a column to the table to account for the preformulated BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] vaccine that will be administered to the expanded-enrollment participants from a preformulated single vial (no dilution required). Clarified text in the footnotes to align with the study design section.	To study a preformulated BNT162b2 bivalent mixture of BNT162b2 Wild Type and BNT162b2 OMI. Administrative change to clarify and align with the study design section.
Section 10.12.6.1 – Study Intervention(s) Administered for Substudy F	Clarified text in the footnotes to align with the study design section.	Administrative change to clarify and align with the study design section.

Amendment 6 (08 Feb 2022)

Overall Rationale for the Amendment:

The primary and secondary objectives and statistical parameters for Substudy D will be modified to include superiority analyses to align with regulatory requirements.

This amendment also includes updates to the inclusion criteria to both Substudy B and Substudy C to reduce the time period of the second dose of prior BNT162b2 to 5 months prior to randomization for all participants. Updates to inclusion criteria for Substudy D and Substudy E were made to increase the eligible population.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Substudy B Design	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 1.1 – Synopsis, Substudy C Design	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization instead of 6 months prior for all participants.	To align with regulatory feedback and current recommendations.
Section 1.1 – Synopsis, Substudy D Design	Updated text to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose. Removed the statement that stratification by age will be managed by the IRT system to ensure a similar distribution of age strata across the 3 cohorts. Updated text to clarify that participants in Cohort 1 will have completed a 2-dose primary series of BNT162b2 (30-µg doses), with their last dose 90 to 240 days prior to enrollment.	To align with regulatory feedback and current recommendations. Text regarding stratification by age was removed as it is already included in the descriptions of the cohorts. To increase the eligible population.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Substudy E Design	Updated text to state that participants who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months prior to randomization, will be enrolled. The previous prior BNT162b2 window was 6 to 12 months.	To increase the eligible population.
Section 10.8.1.2 – Schema for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.1.3 – Schedule of Activities for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.2 – Rationale for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.4 – Study Design for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.8.5.1 – Inclusion Criteria for Substudy B	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 150 days prior to Visit 201 for all participants. Inclusion criterion 1 was combined into a single bullet as this new window applies to all age groups in Substudy B.	To align with regulatory feedback and current recommendations.
Section 10.8.8.3.1 – Substudy B Procedures, Visit 201	Updated text asking to confirm that the participant has only received 2 doses of BNT162b2 at least 5 months prior to randomization.	To align with regulatory feedback and current recommendations.
Section 10.9.1.2 – Schema for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.

Section # and Name	Description of Change	Brief Rationale
Section 10.9.1.3 – Schedule of Activities for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.2 – Rationale for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.3 – Objectives, Estimands, and Endpoints for Substudy C	Updated the control group for noninferiority to age-matched participants randomly selected from C4591001.	To align with the removal of the requirement that participants 12 to 17 years of age must have received 2 prior doses of BNT162b2 in C4591001.
Section 10.9.4 – Study Design for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months prior to randomization instead of 6 months prior for all participants.	To align with regulatory feedback and current recommendations.
Section 10.9.5.1 – Inclusion Criteria for Substudy C	Updated text to clarify that participants may be enrolled if they completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 150 days prior to Visit 301 for all participants. Removed the requirement that participants 12 to 17 years of age must have received 2 prior doses of BNT162b2 in C4591001.	To align with regulatory feedback and current recommendations. To permit enrollment of participants who did not participant in C4591001.
Section 10.9.8.4.1 – Substudy C Procedures, Visit 301	Updated text asking to confirm the participant has only received 2 doses of BNT162b2 at least 5 months prior to randomization.	To align with regulatory feedback and current recommendations.
Section 10.9.9 – Statistical Considerations for Substudy C	Modified the statistical considerations including the hypothesis, general considerations, objectives, estimands, endpoints, and comparisons.	To align with the removal of the requirement that participants 12 to 17 years of age must have received 2 prior doses of BNT162b2 in C4591001.
Section 10.10.1.2.1 – Schema for Substudy D, Participants in Cohorts 1 and 2	Updated text to clarify that Cohort 1 participants must have received 2 doses of BNT162b2 before enrollment (3-8 months after last dose).	To increase the eligible population.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.1.2.2 – Schema for Substudy D, Participants in Cohort 3	Added a footnote to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose.	To align with regulatory feedback and current recommendations.
Section 10.10.1.3.1 – Schedule of Activities for Substudy D, Cohorts 1 and 2	Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs. Updated text to clarify that Cohort 1 participants must have received 2 doses of BNT162b2 before enrollment (3-8 months after last dose).	To provide clarification on expectations for site personnel regarding self-swabs. To increase the eligible population.
Section 10.10.1.3.2 – Schedule of Activities for Substudy D, Cohort 3	Added footnote to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose. Updated the early part of the Visit 506 window to 150 days after Vaccination 2. Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs.	To align with regulatory feedback and current recommendations. To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.10.2.1 – Study Rationale for Substudy D	Corrected “2 doses” to “3 doses” of BNT162b2 OMI.	This was an administrative change to correct a typo.
Section 10.10.3 – Objectives, Estimands, and Endpoints for Substudy D	Updated the primary and secondary objectives. Superiority added as a primary immunogenicity objective. Noninferiority and “super” superiority added as secondary immunogenicity objectives. Exploratory objectives and footnotes were modified.	To align with regulatory requirements.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.4 – Study Design for Substudy D	Updated text to clarify that participants in Cohort 3 may receive their third dose of BNT162b2 OMI as early as 5 months after their second dose. Updated text to clarify that Cohort 1 participants must have received 2 prior doses of 30 µg BNT162b2, with the second dose being 90 to 240 days before Visit 401 (Day 1). Removed the statement that stratification by age will be managed by the IRT system to ensure a similar distribution of age strata across the 3 cohorts.	To align with regulatory feedback and current recommendations. To increase the eligible population. Text regarding stratification by age was removed as it is already included in the descriptions of the cohorts.
Section 10.10.5.1 – Inclusion Criteria for Substudy D	Updated inclusion criteria for Cohort 1 participants to state that participants must have received 2 prior doses of 30 µg BNT162b2, with the second dose being 90 to 240 days before Visit 401 (Day 1).	To increase the eligible population.
Section 10.10.8.6 –Substudy D Procedures	Added details regarding the self-swabs to clarify that sites must provide/ensure the participant has a nasal self-swab kit and provide instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.10.6.1.1 – Administration for Substudy D	Added the following text: Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.	To align with regulatory feedback and current recommendations.
Section 10.10.8.6.2 – Administration of BNT162b2 OMI to COVID-19 Vaccine-Naïve Participants (Cohort 3) for Substudy D	Updated text to clarify that participants will receive 2 doses (primary series) of BNT162b2 OMI, separated by 21 days, with a third dose approximately 5 months later.	Administrative change and to align with regulatory feedback and current recommendations.
Section 10.10.8.6.2.6 – Administration of BNT162b2 OMI to COVID-19 Vaccine-Naïve Participants (Cohort 3), Visit 506 for Substudy D	Updated text to clarify that Vaccination 3 may be administered as early as 5 months (150 days) after Vaccination 2.	To align with regulatory feedback and current recommendations.
Section 10.10.9 – Statistical Considerations for Substudy D	Updated the primary and secondary objectives to include superiority and “super” superiority. Additional changes were made to the statistical hypothesis, multiplicity adjustment, general considerations and comparisons.	To align with regulatory requirements.

Section # and Name	Description of Change	Brief Rationale
Section 10.11.1.3 – Schedule of Activities for Substudy E	Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.11.4 – Study Design for Substudy E	Updated text to state that participants who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months prior to randomization, will be enrolled. The previous prior BNT162b2 window was 6 to 12 months.	To increase the eligible population.
Section 10.11.5.1 – Inclusion Criteria for Substudy E	Updated inclusion criteria to state that participants who have received 3 prior doses of 30 µg BNT162b2, with the third dose being 5 to 12 months before Visit 601 (Day 1). The previous prior BNT162b2 window was 6 to 12 months.	To increase the eligible population.
Section 10.11.8.6 –Substudy E Procedures	Added details regarding the self-swabs to clarify that sites must provide/ensure the participant has a nasal self-swab kit and provide instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.12.1.3 – Schedule of Activities for Substudy F	Added a row for the following procedure: Provide/ensure the participant has a nasal self-swab kit and instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.
Section 10.12.8.5 –Substudy F Procedures	Added details regarding the self-swabs to clarify that sites must provide/ensure the participant has a nasal self-swab kit and provide instructions on self-collection of nasal swabs.	To provide clarification on expectations for site personnel regarding self-swabs.

Amendment 5 (20 Jan 2022)

Overall Rationale for the Amendment:

The SARS-CoV-2 variant B.1.1.529, also known as Omicron, is currently the dominant variant in many countries and within the US is responsible for 95.4% of sequenced COVID-19 cases. Current data note that the vaccine effectiveness against hospitalization is 88% (78%-93%) for Omicron after 3 doses of vaccine. However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the

Delta variant. The addition of a higher-dose booster may improve protection, particularly in older individuals, with increased longevity of an immune response, provided it has a tolerable safety profile. Therefore, Substudies E and F have been designed to evaluate high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2 OMI and BNT162b2 (30 µg of each) compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose.

This amendment also incorporates the addition of a BNT162b2 30-µg dose group (given as a third dose) to Cohort 1 in Substudy D. In this group, 205 participants will be enrolled to provide a contemporaneous third-dose control group for analyses and comparisons.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Sections 1 through 9	Cross-reference to sections within Substudies E and F added where required and throughout.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 1.1 – Synopsis, Substudy D Design	Addition of description of Group 2b (1 dose of BNT162b2), updated total number of participants to 1420, updated Cohort 1 participant total to 615, and updated the table to include Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 1.1 – Synopsis, Substudy D Number of Participants	Updated the number of participants to 615 for Cohort 1.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 1.1 – Synopsis, Overall Design	Addition of design of Substudies E and F, number of participants, and specified that an IRC will be used for Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 1.1 – Synopsis, Substudies E and F Number of Participants	Addition of Substudies E and F, number of participants.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Data Monitoring Committee or Other Independent Data Monitoring Committee	Addition of DMC and IRC details for Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 2.2 – Background	Addition of Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 2.3 – Risk Assessment	Added additional mitigations for Substudies E and F and updated existing mitigations to align with the study designs for Substudies D, E, and F.	Substudies E and F have a higher dose level of study vaccine, and additional mitigations have been put in place. Existing mitigations were updated to account for the dosing schedules for Substudies D, E, and F.
Section 4.3 – Justification for Dose	Addition of justification for dose levels in Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information – Substudy D	Addition of Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information – Substudies E and F	Confirmation of the safety reporting time periods for Substudies E and F.	Substudies E and F have been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Sections 10.7.9.4 – Interim Analysis and 10.7.9.4.1 – Analysis Timing for Substudy A	Removed efficacy and safety analysis when all participants completed blinded follow-up and added that additional analyses may be conducted if required for regulatory purposes. Removed the requirement to conduct interim analyses every 2 months.	This will allow the team to deliver the analysis if required for regulatory purposes. Interim analyses are no longer needed every 2 months as Substudy A has been unblinded.
Section 10.9.6.2.2 – Blinding of the Sponsor for Substudy C	Updated timing for unblinding of the participant to 3 months after study vaccination administration.	This will allow for collection of blinded safety data up to 3 months after study vaccine administration.

Section # and Name	Description of Change	Brief Rationale
Section 10.9.8.4.3 – Study Assessments and Procedures, Visit 303 for Substudy C	Removed text stating that the participant would be unblinded at the 1-month after booster vaccination visit.	Participants will now be unblinded at 3 months after study vaccine administration.
Section 10.9.9.5 – Sample Size Determination for Substudy C	Updated the assumed response rate for each comparative group at the comparative time point from 90% to 95%.	This was a typo in the previous version of the protocol.
Section 10.10.1.2.1 Schema for Cohorts 1 and 2 in Substudy D	Addition of the PBMC and HLA sample collections.	To provide further clarity on all blood sample collections to be performed during the study.
Section 10.10.1.2.2 Schema for Cohort 3 in Substudy D	Addition of the PBMC and HLA sample collections.	To provide further clarity on all blood sample collections to be performed during the study.
Section 10.10.1.2.1 – Participants in Cohorts 1 and 2 for Substudy D	Addition of Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.2.1 – Study Rationale for Substudy D	Addition of description of Group 2b (1 dose of BNT162b2).	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.3 – Objectives, Estimands, and Endpoints for Substudy D	Addition of objectives, estimands, and endpoints for Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.4.1 – Overall Design for Substudy D	Addition of description of Group 2b (1 dose of BNT162b2), updated total number of participants to 1420, updated Cohort 1 participant total to 615, and updated the table to include Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.6.2.2 – Blinding of the Sponsor for Substudy D	Updated timing of participant unblinding for Cohort 2 from Visit 402 to Visit 404 and added that Cohort 1 (Groups 1 and 2b) may also be unblinded at this time.	This will allow for collection of blinded safety data up to 3 months after study vaccine administration. Cohort 1 was added to account for Group 2b being added.
Section 10.10.8.2 – Immunogenicity for Substudy D	Addition of text clarifying that B-cell responses will also be tested.	Testing for B-cell responses was planned but was erroneously not specified in the previous protocol version.
Section 10.10.8.6.1.2 – Visit 402 for Substudy D	Moved the text from Visit 402 to Visit 404 describing unblinding of participants in Cohort 2 and added that Cohort 1 (Groups 1 and 2b) may also be unblinded at this time.	This will allow for collection of blinded safety data up to 3 months after study vaccine administration. Cohort 1 was added to account for Group 2b being added.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.9 – Statistical Considerations for Substudy D	Addition of statistical considerations throughout this section related to Group 2b.	Group 2b has been added to Substudy D to provide a contemporaneous third-dose control group for analyses and comparisons.
Section 10.10.9.5 – Sample Size Determination for Substudy D	Updated the assumed response rate for each comparative group at the comparative time point from 90% to 95%.	This was a typographical error in the previous version of the protocol.
Section 10.11 – Appendix 11: Substudy E	Addition of Substudy E.	Substudy E has been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.
Section 10.12 – Appendix 12: Substudy F	Addition of Substudy F.	Substudy F has been added to evaluate high-dose BNT162b2 OMI, high-dose BNT162b2, and a high-dose combination of BNT162b2 OMI and BNT162b2 given as a fourth dose.

Amendment 4 (22 Dec 2021)

Overall Rationale for the Amendment:

- On 26 November 2021 and 30 November 2021, the WHO and the US, respectively, classified a new SARS-CoV-2 variant, B.1.1.529, a VOC, and named it Omicron. Pfizer has developed a new vaccine, BNT162b2 OMICRON (B.1.1.529) (referred to throughout the protocol as BNT162b2 OMI), which is a BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron B.1.1.529 variant–specific mutations. Substudy D has been designed to assess the safety, tolerability, and immunogenicity of BNT162b2 OMI.

Section # and Name	Description of Change	Brief Rationale
Sections 1 through 9	Cross-reference to sections within Substudy D added where required throughout	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Rationale	Addition of details on current VOCs	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Overall Design	Addition of design of Substudy D and number of participants	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Substudy B Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series	This change has been implemented to enable these participants to enroll in this substudy sooner and because of

Section # and Name	Description of Change	Brief Rationale
	of BNT162b2 (30-µg doses) prior to randomization in this substudy	the emergence of the new VOC, Omicron
Section 1.1 - Synopsis, Substudy C Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 2.2 – Background	Addition of Substudy D	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 2.2.1 - Clinical Overview	Details of EUA for a booster dose in the US, EU, and other countries as well as details of the interim safety and efficacy analysis results for C4591031 Substudy A	This change has been implemented to reflect current recommendations and to provide details of the recent interim safety and efficacy analysis results for C4591031 Substudy A
Section 6.6 - Continued Access to Study Intervention After the End of the Study	Confirmation that if the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose	To ensure that participants are vaccinated with the currently approved dose and details can be entered on their vaccination records (eg, CDC card)
Section 8.1.1 - Biological Samples	Added detail that no testing of the participants' genetic testing is performed, with the exception of those participants who have provided specific consent to genetic testing samples of the blood for PBMC isolation and HLA typing	Inclusion of PBMC and HLA testing in Substudy D
Section 8.2.4.2 - Local Reactions	Confirming that a reaction classified as Grade 4 should be reported as an AE in the CRF	A confirmed Grade 4 reaction should be reported as an AE in the CRF
Section 8.3.1 - Time Period and Frequency for Collecting AE and SAE Information	Confirmation of the safety reporting time periods for Substudy D	Substudy D has been added because of the emergence of the new VOC, Omicron
Section 10.7.8.5.8.3 - Visit 103	Removal of the request to contact the site for any medically attended events or respiratory symptoms after the final visit	To remove bullets entered in error
Section 10.8.1.2 - Schema	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.1.3 - Schedule of Activities for Substudy B	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.2.1 - Study Rationale	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series	This change has been implemented to enable these participants to enroll in this substudy sooner and because of

Section # and Name	Description of Change	Brief Rationale
	of BNT162b2 (30-µg doses) prior to randomization in this substudy	the emergence of the new VOC, Omicron
Section 10.8.4.1 - Overall Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.5.1 - Inclusion Criteria	Updated the inclusion window for 12- to 17-year-olds from 365 days to 240 days after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.8.8.3.1 - Visit 201 – Vaccination (Day 1)	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Sections 10.8.8.3.7 and 10.9.8.5.1- Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction	Deletion of the temperature reference in the sections to ensure consistency with Section 8.2.4.4	To ensure consistency within the protocol
Section 10.9.1.2 - Schema	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.1.3 - Schedule of Activities for Substudy C	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.2.1 - Study Rationale	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.3 - Objectives, Estimands, and Endpoints	Added an exploratory objective to describe the immune response to VOCs with an endpoint of SARS-CoV-2 neutralizing titers for VOCs	To examine the breadth of neutralizing titers against VOCs
Section 10.9.4.1 - Overall Design	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron

Section # and Name	Description of Change	Brief Rationale
Section 10.9.5.1 - Inclusion Criteria	Updated the inclusion window for 12- to 17-year-olds from 365 days to 240 days after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.8.4.1 - Visit 301 – Vaccination (Day 1)	Updated the inclusion window for 12- to 17-year-olds from 12 months to 8 months after completion of a 2-dose primary series of BNT162b2 (30-µg doses) prior to randomization in this substudy	This change has been implemented to enable these participants to enroll in this substudy sooner and because of the emergence of the new VOC, Omicron
Section 10.9.6.2.2 - Blinding of the Sponsor	Clarification that once a participant has completed their 1-month visit, they may be unblinded to confirm the dose of BNT162b2 received. The study team will also become unblinded to the participant's original study intervention allocation at this time	If the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose to ensure that the participant is vaccinated with the currently approved dose and details can be entered on their vaccination records (eg, CDC card)
Section 10.9.8.4.3 - Visit 303	Clarification that once a participant has completed their 1-month visit, they may be unblinded to confirm the dose of BNT162b2 received. The study team will also become unblinded to the participant's original study intervention allocation at this time	If the 10-µg dose is found to have a suboptimal immune response, as determined by the sponsor, this group will be offered a single 30-µg dose to ensure that the participant is vaccinated with the currently approved dose and details can be entered on their vaccination records (eg, CDC card)
Section 10.9.8.5 - Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Deletion of reference to troponin blood samples collected during the study	These samples are not collected as part of Substudy C
Section 10.9.9.3.4 - Exploratory Endpoint(s) Analysis	Addition of an exploratory immunogenicity objective	To examine the breadth of neutralizing titers against VOCs in the 2 dose levels
Section 10.10 - Substudy D	Addition of Substudy D	Newly included substudy

Amendment 3 (28 Oct 2021)

Overall Rationale for the Amendment:

- Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Substudy B is added to assess the safety and tolerability of a booster (third) dose of BNT162b2 through the potential analysis of serum troponin levels.

- Substudy C is added to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg and at 30 µg. The key objective of the study is to demonstrate that the immune response induced by a booster (third) dose of BNT162b2 at a 10-µg dose is noninferior to the immune response elicited 1 month after the second dose of BNT162b2 at 30 µg (ie, having completed a 2-dose primary series of BNT162b2 [30-µg doses]).

Section # and Name	Description of Change	Brief Rationale
Sections 1 through Section 9	Cross-reference to sections within Substudy B and Substudy C added where required throughout	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 1.1 - Synopsis	Addition of design of Substudy B and Substudy C, number of participants, and use of a DMC (Substudy C only)	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 2 - Introduction and Section 2.2 - Background	Addition of text reporting that BNT162b2 has been fully licensed for use in individuals 16 years of age and above in the US as of 23 Aug 2021	This change has been implemented to reflect current recommendations
Section 2.2 - Background	Addition of Substudy B and Substudy C	Substudy B and Substudy C have been added in response to commitments made to CBER
Sections 5.1 and 5.2 - Inclusion and Exclusion Criteria	Addition of inclusion and exclusion criteria specific to Substudy B and Substudy C	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 7.2 - Participation Discontinuation/ Withdrawal From Study	Confirmation that receipt of a nonstudy COVID vaccine during study participation will result in study withdrawal	This update was implemented to clarify participant withdrawal criteria
Section 7.2.1 - Withdrawal of Consent	Addition of text to confirm that if a participant wishes to receive a COVID-19 vaccine outside of the study, he or she may request to know which study intervention he or she received without needing to reconsent	This update was implemented to allow participants to be unblinded if they want to receive a COVID-19 vaccine outside of the study
Section 8.2.4 - Electronic Diary - Applicable Only to Substudy B and Substudy C	Addition of details for reactogenicity e-diary use	This section was added to describe the use of a reactogenicity e-diary for substudies that will utilize one
Section 8.3.1 - Time Period and Frequency for Collecting AE and SAE Information	Confirmation of the safety reporting time periods for Substudy B and Substudy C	Substudy B and Substudy C have been added in response to commitments made to CBER
Section 8.3.5.1 - Exposure During Pregnancy	Confirmed that any pregnancy that occurs 28 days after the last dose of study intervention will not be considered EDP for this study	This change has been implemented to align with contraception requirements
Section 10.8 - Substudy B	Addition of Substudy B	Newly included substudy
Section 10.9 - Substudy C	Addition of Substudy C	Newly included substudy

Amendment 2 (27 Aug 2021)

Overall Rationale for the Amendment:

- Addition of procedures for monitoring potential myocarditis or pericarditis in response to commitments made to CBER and administrative updates.

- Addition of wording that participants randomized to receive placebo at the booster dose vaccination visit may be offered the opportunity to receive BNT162b2 at a determined time frame at the discretion of the sponsor.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 2.3.1 – Risk Assessment	Addition of myocarditis and pericarditis	This update has been implemented in response to commitments made to CBER
Section 5 – Study Population	Addition of wording on diversity of recruitment	This addition was implemented for the collection of race and ethnicity data in prescreeners to reflect the enrollment of a diverse participant population
Section 5.2 – Exclusion Criteria	Exclusion criterion 13 edited to change the exclusion timeframe from the duration of study participation to within 28 days of confirmed receipt of BNT162b2	This criterion was changed to allow study participants to enroll in other clinical trials before the end of their study participation
Section 8.2.5– Pregnancy Testing	Clarified the timing of pregnancy tests	This update addresses discrepancies with SoA
Section 8.3.8 – Adverse Events of Special Interest	Addition of myocarditis and pericarditis	This update has been implemented in response to commitments made to CBER
Section 10.1.3 – Informed Consent Process	Clarified that assent must be obtained when the participant has the capacity to provide assent	This update has been made to ensure compliance with IRB./ECs
Section 10.7.1.3.1 – Administration of BNT162b2 to Those Originally Assigned to Placebo	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 10.7.4.1 – Overall Design	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 10.7.6.2.1 – Blinding of Site Personnel	Addition of wording on unblinding decisions	This addition was implemented to allow the sponsor to be unblinded outside of the interim analyses
Section 10.7.6.2.2 – Blinding of the Sponsor	Addition of wording on unblinding decisions	This addition was implemented to allow the sponsor to be unblinded outside of the interim analyses

Section # and Name	Description of Change	Brief Rationale
Section 10.7.8.5 – Study Procedures	Addition of a procedure to any visit that occurs sooner than 1 month after any vaccination	This update has been implemented in response to commitments made to CBER
Section 10.7.8.5.1 – Visit 1 – Booster Vaccination (Day 1)	Clarified wording on site staff roles in relation to randomization and study intervention allocation number assignment	This update has been made to ensure the blind is maintained by the investigator site staff
Section 10.7.8.5.8 – Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo	Addition of wording on the timing of providing booster doses to placebo participants	This update was implemented to clarify the timing of booster vaccination for placebo participants
Section 10.7.8.5.9 – Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	Addition of an unplanned visit to capture data pertaining to myocarditis and pericarditis	This visit has been implemented in response to commitments made to CBER
Section 10.8 – Appendix 8: Protocol Amendment History	Addition of Appendix 8 to include the protocol amendment history, and moved the Protocol Amendment Summary of Changes Table for Protocol Amendment 1 from the beginning of the document to this new section	This update has been made to ensure only the latest Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents

Amendment 1 (27 May 2021)

Overall Rationale for the Amendment: Correction to exclusion criterion and administrative update.

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Removal of exclusion criterion 9: Previous participation in other studies involving study intervention containing LNPs.	Included in the original protocol in error. C4591031 Substudy A aims to enroll participants having previously received BNT162b2 in Study C4591001.
5.2. Exclusion Criteria	Addition of new exclusion criterion (Number 9) to exclude participants having previously received a COVID-19 vaccine other than BNT162b2.	To exclude participants who have received anything more than 2 doses of only BNT162b2 COVID-19 vaccine.
10.7.4.1. Overall Design	Update to cutoff values for age strata from ≥16 to <55 and ≥55 years of age to ≥16 to 55 and >55 years of age.	To ensure the age strata match those used in Study C4591001.
10.7.9.5. Sample Size Determination	Update to the expected number of cases in Table 1 from 97 to 98 at 7 days to 6 months if nonboosted and IR0 = 0.14/pyr.	To address prior rounding error.

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BNT162b2 OMI	BNT162b2 OMICRON (B.1.1.529)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
E1, E2, E3, E4	Estimand 1, Estimand 2, Estimand 3, Estimand 4
e-diary	electronic diary
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration

Abbreviation	Term
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G
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	independent review committee
IRT	interactive response technology
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
N	SARS-CoV-2 nucleoprotein

Abbreviation	Term
N/A	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
OMI	Omicron (ie, in BNT162b2 OMI)
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PACL	protocol administrative change letter
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SSD	Substudy D
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCR	T-cell receptor
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAED	vaccine-associated enhanced disease
VE	vaccine efficacy
VOC	variant of concern
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

10.15. Appendix 15: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria:

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg-negative, anti-HBe–positive;
- Serum HBV DNA <2000 IU/mL;
- Persistently normal ALT and/or AST levels;
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

10.16. Appendix 16: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.

- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

  - Samples for specified genetic analysis (see Section 10.10.8.5 and Section 10.11.8.5) will be stored for up to 15 years or other period as per local requirements.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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Protocol C4591031 – Substudy A

A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 – SUBSTUDY A

Statistical Analysis Plan (SAP)

Version: 1

Date: 30 Jun 2021

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 30 Jun 2021	Protocol Amendment 1, 27 May 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in C4591031 – Substudy A. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective in Substudy A are described in Table 2 below.

In the primary safety objective evaluations, missing AE start 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 efficacy objectives are based on the evaluable efficacy population (see Section 4 for definition). These estimands estimate VE in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by the all-available efficacy (mITT) population. Missing laboratory results will not be imputed for the efficacy endpoints.

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Efficacy	**Primary Efficacy**	**Primary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose	• AEs • SAEs
Secondary Efficacy	**Secondary Efficacy**	**Secondary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against asymptomatic infection in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion
Exploratory		
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received the BNT162b2 booster dose	In participants who received BNT162b2 at the booster vaccination (at initial randomization and subsequently): Incidence per 1000 person-years of follow-up	Confirmed COVID-19 incidence per 1000 person-years of the entire study follow-up period

2.2. Study Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥16 to 55 years of age and approximately 40% of participants >55 years of age. Approximately 10,000 participants will be randomized in the study. Assuming a 15% nonevaluable rate, there will be approximately 4250 evaluable participants in each group.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses further detailed in Section 7. The timing of this booster vaccination will also be informed by the outcome of the interim analyses detailed in Section 7.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Efficacy Endpoint

- Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

3.1.2. Safety Endpoints

- AEs from the booster dose to 1 month after the booster dose
- SAEs from the booster dose to 6 months after the booster dose

3.1.2.1. Adverse Events

AEs will be assessed from the time of informed consent through Visit 2 (approximately 1 month after the booster vaccination), and from Visit 101 to Visit 102 (approximately 1 month after participants who originally received placebo are administered BNT162b2). AEs will be categorized according to MedDRA terms.

The primary safety endpoints will be summarized by SOC and PT at the participant level.

The primary safety endpoints will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose).

AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

A 3-tier approach will be used to summarize AEs from booster vaccination through Visit 2. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. No Tier 1 events have been identified to date for BNT162b2.

- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 1% of participants with the AE term in at least 1 vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

3.1.2.2. Serious Adverse Events

SAEs will be assessed from the time of informed consent to Visit 3 (approximately 6 months after the booster vaccination), and from Visit 101 to 103 (approximately 6 months after participants who originally received placebo are administered BNT162b2). SAEs will be categorized according to MedDRA terms.

The primary safety endpoints will be summarized by SOC and PT at the participant level. Additionally, the SAEs will be listed.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

- Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

- Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion

3.3. Exploratory Endpoints

3.3.1. Efficacy Endpoint

- Confirmed COVID-19 incidence per 1000 person-years of the entire study follow-up period

3.4. Baseline and Other Variables

Measurements or samples collected prior to booster vaccination at Visit 1 are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at booster vaccination (in years), sex (male or female), BMI, race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the time of vaccination (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 19th birthday, the participant is considered to be 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at booster vaccination for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA. Comorbidities that may increase the risk for severe COVID-19 illness will be categorized based on medical history terms.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed and any findings will be recorded in the source documents and clinically significant findings, if any, will be recorded on the medical history CRF.

3.4.2. Prior/Concomitant Vaccines and Concomitant Medications

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

- Any vaccinations received from 28 days prior to study enrollment until 28 days following administration of the last study intervention.
- Prohibited medications listed in Protocol Section 6.8.1 will be recorded to include start and stop dates, name of the medication, dose, unit, route, and frequency.

Prior and concomitant vaccines and concomitant medications will be coded using WHO DDE.

3.5. Safety Endpoints

AEs and SAEs have been described above in the primary safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per SOPs.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable efficacy	All eligible randomized participants who receive the booster vaccination as randomized and have no other important protocol deviations as determined by the clinician.
All-available efficacy (mITT)	All randomized participants who receive at least 1 dose of the study intervention.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of efficacy, eg, participant receipt of a medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received.

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the vaccine group to which they were randomized.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. 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.

The majority of Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The study will be unblinded to all sponsor/Pfizer staff at a time informed by the outcome of the interim analyses as detailed in Section 7. Further details can be found in Protocol Section 10.7.6.2.

5.1. Hypotheses and Decision Rules

All objectives in this substudy are descriptive. No hypothesis testing is planned.

No multiplicity adjustment is applied for the study as there is no statistical hypothesis.

5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method.[2] In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

5.2.2. Analyses for Count Data

Descriptive statistics for count data are incidence rate, the numerator (number of events observed) and the denominator (total person-years of follow-up) used in the incidence rate calculation, and the 95% CIs where applicable.

The exact 95% CI for incidence rates for each group will be computed using the method of Ulm[3] based on the link between the chi-square distribution and the Poisson distribution.

5.2.3. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant, following the Pfizer standard of handling incomplete AE start dates. A complete missing start date for an AE is not allowed in the data collection.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Vaccine Efficacy Endpoint

6.1.1.1. Confirmed COVID-19 Incidence From 7 Days After the Booster Dose per 1000 Person-Years of Blinded Follow-up

6.1.1.1.1. Main Analysis

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).
- Analysis time points: At interim analyses and at the end of the surveillance period (blinded follow-up).
- Analysis methodology: VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of COVID-19 illness rate per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose (see Appendix 2 for details on the derivation of IRR and VE). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.
- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.1.1.1.2. Supplementary Analyses

A descriptive summary of VE over different time intervals (ie, through 2 months, from 2 to 4 months, and from 4 to 6 months after the booster dose, etc), along with the associated 2-sided 95% CI, will also be calculated using the same method.

VE by time between Dose 2 of the primary vaccination series and the booster dose (eg, 6-8 months, 8-10 months, 10-12 months after Dose 2) will also be summarized descriptively. Kaplan-Meier cumulative incidence curves will be provided.

6.1.2. Safety Endpoints

6.1.2.1. Adverse Events

6.1.2.1.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the booster dose to 1 month after the booster dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Booster dose to 1 month after the booster dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1) and an additional 3-tier approach (Section 3.1.2.1).
- Intercurrent events and missing data: Partial AE start dates will be imputed using the Pfizer standard algorithm.
- Reporting results: AEs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers (Section 3.1.2.1). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the active vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[2] method will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within the SOC. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs, by each SOC and each PT within the SOC for each vaccine group.

6.1.2.1.2. Supplementary Analyses

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.2.2. Serious Adverse Events

6.1.2.2.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from the booster dose to 6 months after the booster dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Booster dose to 6 months after the booster dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: Partial SAE dates will be imputed using the Pfizer standard algorithm.

- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs will be provided for each vaccine group.

6.2. Secondary Endpoint(s)

6.2.1. Secondary Efficacy Endpoints

6.2.1.1. Confirmed Severe COVID-19 (Based on FDA Definition) Incidence From 7 Days After the Booster Dose per 1000 Person-Years of Blinded Follow-up

6.2.1.1.1. Main Analyses

- Estimands:
    - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
    - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).

- Analysis time point: End of the surveillance period (blinded follow-up).

- Analysis methodology: VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed severe COVID-19 illness rate (based on FDA definition) per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose (see Appendix 2 for details on the derivation of IRR and VE). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.

- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.

- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.2.1.2. Confirmed Severe COVID-19 (Based on CDC Definition) Incidence From 7 Days After the Booster Dose per 1000 Person-Years of Blinded Follow-up

6.2.1.2.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).
- Analysis methodology: VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed severe COVID-19 illness rate (based on CDC definition) per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose (see Appendix 2 for details on the derivation of IRR and VE). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.
- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.2.1.3. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up Based on N-Binding Antibody Seroconversion

6.2.1.3.1. Main Analyses

- Estimand:
  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection for the active vaccine group to the placebo (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).

- Analysis time point: End of the surveillance period.

- Analysis methodology: An asymptomatic case of SARS-CoV-2 infection (Appendix 3) based on the seroconversion of N-binding antibody is defined as positive N-binding antibody at Visit 3 in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.

- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.

- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.3. Exploratory Endpoints

6.3.1. Vaccine Efficacy Endpoint

6.3.1.1. Confirmed COVID-19 Incidence per 1000 Person-Years of the Entire Study Follow-up Period

6.3.1.1.1. Main Analyses

- Estimand:

    - Incidence of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of the entire study follow-up period in participants who received BNT162b2 at the booster vaccination at initial randomization and subsequently, respectively (Section 2.1).

- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4). For participants who were randomized to placebo and subsequently received BNT162b2, the time of receipt of BNT162b2 will be considered as baseline. All rules for determining evaluable efficacy and all-available efficacy (mITT) populations will be similarly applied.

- Analysis time point: End of the surveillance period.

- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and exact 2-sided 95% CI based on Poisson distribution (Section 5.2.2) for confirmed COVID-19 illness from 7 days after the booster vaccination will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.

- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.

- Reporting results: Incidence rate and the associated 2-sided 95% CIs and Kaplan-Meier cumulative incidence curves will be provided.

6.4. Subgroup Analysis

Subgroup analyses based on age, race, ethnicity, sex, and country will be performed on all primary and secondary safety and efficacy endpoints (as supplemental analyses).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age, sex, race, ethnicity, and classification of BMI, will be summarized for the safety population for each vaccine group and overall.

6.5.1.2. Medical History

Each reported medical history term will be mapped to an SOC and PT according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group for the overall safety population.

The number and proportion of participants with comorbidities that may increase the risk for severe COVID-19 illness will be summarized by each vaccine group.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received the booster vaccination, who completed the follow-up visits, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately, along with the reasons for exclusion, by vaccine group.

Participants' follow-up time after completion of vaccinations will be summarized by vaccine group.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving the booster dose, as well as the time between the booster dose and the doses of BNT162b2 prior to randomization, will be tabulated for each vaccine group and overall for all randomized

participants. The denominator for the percentages is the total number of randomized participants in the given vaccine group or overall.

In addition, the relation of randomized vaccine to actual vaccine received will be presented as a cross tabulation of the actual vaccine received versus the randomized vaccine.

A listing of participants showing the randomized vaccine and the vaccine actually received will be presented.

6.5.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification. All vaccines received within 28 days prior to study enrollment until 28 days following administration of the last study intervention will be listed. The number and percentage of participants receiving each concomitant vaccine after the booster vaccination will be tabulated by vaccine group. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analyses

AE and SAE summaries and analyses are described under Primary Endpoint(s) in Section 6.1.

7. INTERIM ANALYSES

7.1. Introduction

Interim efficacy analyses will be performed every 2 months by an unblinded statistical team to inform the timing of administration of BNT162b2 to those originally assigned to placebo. The first interim analysis will be performed after all participants reach 2 months of blinded follow-up. The final efficacy analyses to assess the primary and secondary efficacy objectives are planned to be conducted when all participants complete blinded follow-up (planned be approximately 175 days after the vaccination at Visit 1, but could be earlier or later depending on outcome of the interim analyses).

At each interim analysis, the following 2 estimates of VE will be obtained: (1) VE of the BNT162b2 booster group to the nonbooster group (placebo), which is the primary estimand defined for this substudy and directly estimable using the data observed in this substudy, and (2) VE of the nonbooster group (received primary series of 2 doses of BNT162b2 approximately 6 months prior to enrollment in this study and did not receive BNT162b2 booster) relative to an unvaccinated population (never received BNT162b2 primary series, not observable in this study). These estimates will be obtained using the following derivations.

Let .. $_{12}$ be the VE of the BNT162b2 booster group relative to the nonbooster group, VE_1 be the VE of the BNT162b2 booster group relative to an unvaccinated population, VE_2 be the VE of the nonbooster group relative to an unvaccinated population, IR_1 be the incidence rate of COVID-19 illness in the BNT162b2 booster group, IR_2 be the incidence rate of

COVID-19 illness in the placebo booster group, and IR_0 be the nonobservable incidence rate in the unvaccinated population.

(1) VE_{12} can be estimated by observed IR_1 and IR_2 in the study as $VE_{12} = 1 - \frac{IR_1}{IR_2}$;

Since $VE_1 = 1 - \frac{IR_1}{IR_0}$, $VE_2 = 1 - \frac{IR_2}{IR_0}$,

(2) VE_2 can then be estimated by observed IR_1 and IR_2 in the study and an assumed VE_1 as

$VE_2 = 1 - \frac{IR_2(1-VE_1)}{IR_1}$.

Although VE_1 is also not observable from the study, it is expected that VE after the booster dose will be similar to that after the first 2 vaccine doses. Based on the results of the updated efficacy analyses from Study C4591001, the VE from 7 days to 2 months, from 2 to 4 months, and from 4 to 6 months after Dose 2 were approximately 96%, 90%, and 84%, respectively. After 6 months, a 6% drop in VE every 2 months will be assumed. These assumed values of VE_1 will be used to estimate VE_2 at the interim analyses.

If the point estimate of VE_2 (nonbooster group relative to unvaccinated population) in a 2-month interval (ie, 7 days to 2 months, 2 to 4 months, etc) at an interim analysis is <60%, the study will be unblinded, and the placebo group participants may receive BNT162b2 earlier than approximately 175 days after the vaccination at Visit 1. If VE_2 remains ≥60% at the interim analyses, all participants may remain blinded in the study and placebo recipients may not be offered BNT162b2 booster until the 12-month visit. In addition, the placebo group participants may not receive BNT162b2 as part of the study if VE_2 is ≥60% at the final analysis.

7.2. Analysis Timing

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

- Interim efficacy analyses after all participants reach 2 months of blinded follow-up and every 2 months afterwards
- Efficacy and safety analysis when all participants completed the blinded follow-up
- Efficacy and safety analysis at the end of the study

7.3. Data Monitoring Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

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

- Contemporaneous review of related AEs up to 1 month after the booster vaccination
- Contemporaneous review of all SAEs up to 6 months after the booster vaccination
- At the time of the planned interim analyses, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

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

8. REFERENCES

1. Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

3. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990;131(2):373-5.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DBP	diastolic blood pressure
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
HR	heart rate
ICD	informed consent document
ICU	intensive care unit
IRR	illness rate ratio
IWR	interactive Web-based response
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
PaO_2	partial pressure of oxygen, arterial
PT	preferred term
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
VE	vaccine efficacy
WHO DDE	World Health Organization Drug Dictionary Enhanced

Appendix 2. IRR and VE Derivation

COVID-19 Case Definition

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

Confirmed COVID-19: presence of at least 1 of the following symptoms and positive SARS-CoV-2 NAAT during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

- Confirmed severe COVID-19 (FDA definition; listed at https://www.fda.gov/media/139638/download): confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
  - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction*;
  - Admission to an ICU;

- Death.

Confirmed severe COVID-19 (CDC definition; listed at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html): confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Admission to the ICU;
- Intubation or mechanical ventilation;
- Death.

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

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Surveillance Times

Fundamental to this VE trial is the surveillance for cases satisfying various endpoints within each participant that may occur during the trial. Endpoint and participant combinations where surveillance is applicable require identification of the start and the end of the surveillance period in order to determine the participant-level endpoint surveillance time. For all VE-related endpoints in this study, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy	Booster dose + 7 days
All-available efficacy (mITT)	Booster dose + 7 days

For all VE-related endpoints in this study, the end of the surveillance period for each participant is the earliest of the following events:

- When the first COVID-19 case occurs.
- When the end of the study for the participant occurs due to, eg, withdrawal, death, or trial completion, etc.
- When the participant has their first important protocol violation (only for analysis based on the evaluable efficacy population).

- When the participant is unblinded at the time informed by the outcome of the interim analyses for receipt of BNT162b2 or other reasons.

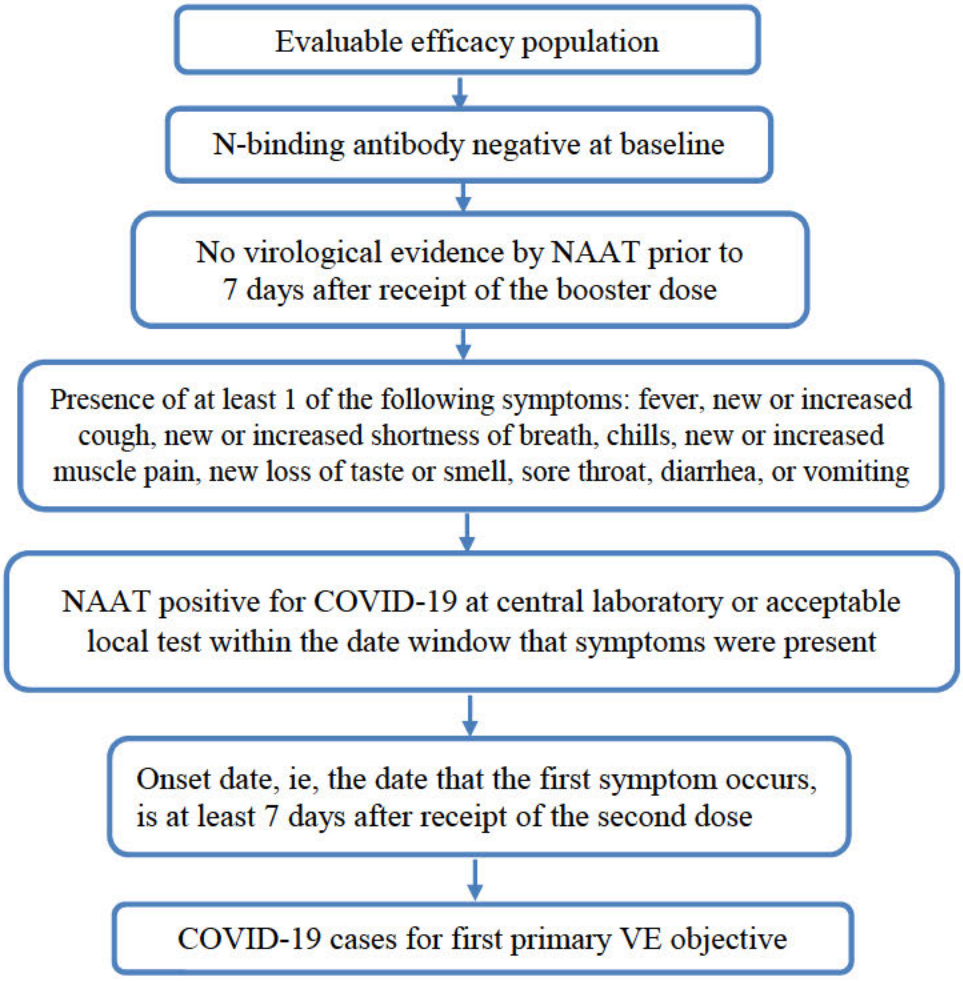
For descriptive assessment of exploratory endpoints of COVID-19 incidence rate through the entire study follow-up period, the surveillance period is defined the same way except that unblinding will not be considered as the end of the surveillance period.

Specific information regarding VE-related endpoint surveillance start and end times by endpoint will be provided in the analysis and reporting plan specification documents.

Once the COVID-19 cases and surveillance period have been identified, VE can be calculated as 100 × (1 – IRR), where IRR is the ratio of confirmed COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group.

Flowchart

1. The flowchart for deriving the COVID-19 cases included below for the first primary endpoints in evaluable efficacy participants with no serological or virological evidence of past SARS-CoV-2 infection:



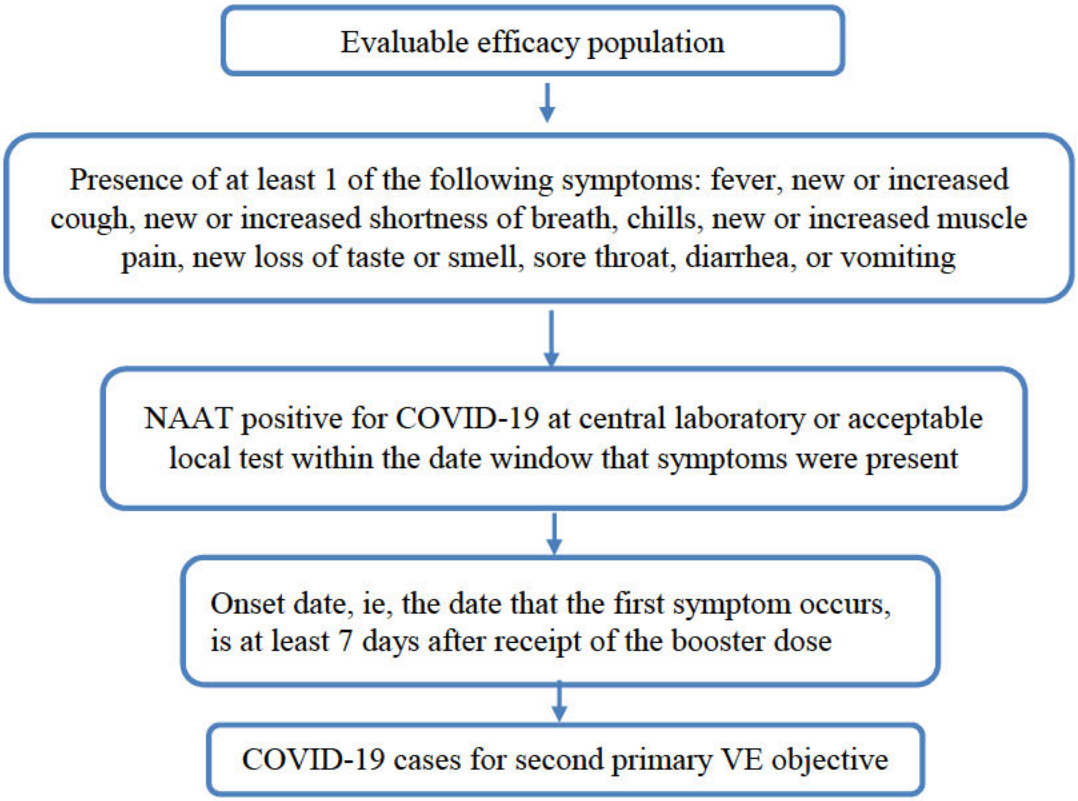
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

b. Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)

c. Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

2. The flowchart for deriving the COVID-19 cases included below for the second primary endpoints in evaluable efficacy participants:



Appendix 3. Asymptomatic Case Based on N-Binding Antibody Seroconversion

Asymptomatic Case Definition

Blood samples for assessment of N-binding antibodies are drawn at Visits 1, 3, and 101 (for participants who originally received placebo and subsequently received BNT162b2). An asymptomatic case of SARS-CoV-2 infection based on the seroconversion of N-binding antibody is defined as positive N-binding antibody at Visit 3 or Visit 101 in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and at the time of a potential COVID-19 illness).

Surveillance Times

For the asymptomatic cases based on N-binding antibody seroconversion, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy	Booster dose
All-available efficacy (mITT)	Booster dose

The end of the surveillance period for each participant is earliest of the following events:

- Date of the first positive N-binding antibody test after the booster vaccination.
- Date of the participant's last post–booster dose N-binding antibody test which is prior to a COVID-19 symptom associated with a non-negative NAAT result.
- Date of the participant's last post–booster dose N-binding antibody test which is on or before an important protocol violation (for analysis based on the evaluable efficacy population).

Protocol C4591031 – Substudy E

A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 – SUBSTUDY E

Statistical Analysis Plan
(SAP)

Version: 2

Date: 20 May 2022

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 07 Mar 2022	PA7-17 Feb 2022	N/A	N/A
2/ 20 May 2022	PA9-03 May 2022	Added 18- to 55-year age cohort and modified objectives	1. Added 18- to 55-year age cohort with 3 treatment arms (bivalent BNT162b2 and BNT162b2 OMI at 60 µg [30 µg each], bivalent BNT162b2 and BNT162b2 OMI at 30 µg [15 µg each], and BNT162b2 OMI at 60 µg at 3:1:2 ratio) in Section 2.3. 2. Modified primary, secondary, and exploratory objectives, estimands, and endpoints in Section 2.2 and Section 3 Modified seroresponse definition in Section 2.2 3. Modified hypotheses, decision rules, and multiplicity analysis in Section 5.1 4. Modified analyses in Section 6 accordingly based on PA9 5. Removed analysis timing at 7 days for safety and immunogenicity in Section 7.3

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591031 – Substudy E. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objectives in Substudy E are described in Table 2 below.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules (Section 5.3). No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Safety		
To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose to BNT162b2-experienced participants >55 years of age	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2 OMI 60 µg and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants 18-55 years of age	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination • Percentage of participants with elevated troponin I levels before and 3 days after study vaccination (sentinel cohort only)	• 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 • Troponin I level (sentinel cohort only)

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Immunogenicity		
G3vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
G4vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
G5vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
G6vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
Secondary Immunogenicity		
G5vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain–neutralizing titers
G6vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain–neutralizing titers
To demonstrate the 'super' superiority of anti-Omicron immune responses after 1 dose of BNT162b2 OMI at 30 µg (G3vG1B), BNT162b2 OMI at 60 µg (G4vG1B), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (G5vG1C), or bivalent BNT162b2 and BNT162b2 OMI at 60 µg (G6vG1C) compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	Same as GMR estimand of G3vG1A, G4vG1A, G5vG1A, and G6vG1A	• SARS-CoV-2 Omicron-neutralizing titers

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Exploratory		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose in BNT162b2-experienced participants >55 years of age	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponsea at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
To describe immune response to bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg), BNT162b2 OMI 60 µg, and BNT162b2 30 µg[b] given as a fourth dose in BNT162b2-experienced participants 18-55 years of age	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponse[a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
To describe the immune response to the reference strain and VOCs for participants[c] in sentinel cohorts of each age group		SARS-CoV-2–neutralizing titers for the reference strain and VOCs
To describe the immune response to any VOCs not already specified in each age group		SARS-CoV-2–neutralizing titers for any VOCs not already specified
To describe confirmed COVID-19 and severe COVID-19 cases in each age group		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group for each age group		

a. Seroresponse is defined as achieving ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of >4 × LLOQ is considered seroresponse.

b. A subset of participants that received BNT162b2 30 µg as fourth dose will be randomly selected from Substudy D Cohort 2 for this objective.

c. This subset of participants will not contribute to the assessment of primary immunogenicity objectives.

2.3. Study Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI (60 µg [30 µg each], given as a single dose). Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months prior to randomization, will be enrolled at investigator sites in the US only. Participants >55 years of age will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 601 as a fourth dose. Participants 18 to 55 years of age will be randomized to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or BNT162b2 OMI at 60 µg at Visit 601 as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open label) of 20 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 90 sentinel cohort participants. An IRC will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 300 participants per group upon confirmation of an acceptable safety assessment.

If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50 µg dose levels of BNT162b2, BNT162b2 OMI, and combination of BNT162b2 and BNT162b2 OMI (25 µg each).

For participants 18 to 55 years of age, sentinel cohorts (sponsor open-label) of 30 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 15 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 75 sentinel-cohort participants. An IRC will review all reported AEs, reactogenicity e-diary data, and troponin levels from the sentinel cohorts collected through Day 7 to allow expanded enrollment upon confirmation of an acceptable safety assessment. An additional 900 participants will be enrolled and randomized in 3:1:2 ratio to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg.

Table 3 and Table 4 describe the enrollment of the sentinel cohorts and steps to progress to expanded enrollment for the >55-year age groups and 18- to 55-year age groups, respectively.

Table 3. Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment

Initial-Sentinel Enrollment[a]		
Study Intervention	**Number of Participants**	**Group Number**
BNT162b2 30 µg (participants >55 years of age)	5	G1
BNT162b2 60 µg (participants >55 years of age)	5	G2
BNT162b2 OMI 30 µg (participants >55 years of age)	5	G3
BNT162b2 OMI 60 µg (participants >55 years of age)	5	G4
Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[b] (participants >55 years of age)	5	G5
Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[b] (participants >55 years of age)	5	G6
Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants		
Expanded-Sentinel Enrollment[a]		
Study Intervention	**Number of Participants**	**Group Number**
BNT162b2 30 µg (participants >55 years of age)	15	G1
BNT162b2 60 µg (participants >55 years of age)	15	G2
BNT162b2 OMI 30 µg (participants >55 years of age)	15	G3
BNT162b2 OMI 60 µg (participants >55 years of age)	15	G4
Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[b] (participants >55 years of age)	15	G5
Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[b] (participants >55 years of age)	15	G6
IRC review of all reported adverse event and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.		
Expanded Enrollment[c]		
Study Intervention	**Number of Participants**	**Group Number**
BNT162b2 30 µg (participants >55 years of age)	300	G1
BNT162b2 60 µg (participants >55 years of age)	300	G2
BNT162b2 OMI 30 µg (participants >55 years of age)	300	G3
BNT162b2 OMI 60 µg (participants >55 years of age)	300	G4

Table 3. Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment

Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[d] (participants >55 years of age)	300	G5
Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[d] (participants >55 years of age)	300	G6

Abbreviation: IRC = independent review committee.

a. Sentinel cohorts will be sponsor open label.
b. Initial- and expanded-sentinel enrollment participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive doses that are prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine.
c. If the IRC's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).
d. Expanded-enrollment participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required.

Table 4. Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment

Initial-Sentinel Enrollment[a,b]			
Group	**Study Intervention**	**Number of Participants**	**Group Number**
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	5	G7
8	Bivalent BNT162b2 and BNT162b2 30 µg (15 µg each) (participants 18 to 55 years of age)	5	G8
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	5	G9
Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants			
Expanded-Sentinel Enrollment			
Group	**Study Intervention**	**Number of Participants**	**Group Number**
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	25	G7
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	25	G8
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	25	G9
IRC review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.			

Table 4. Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment

Expanded Enrollment[c]			
Group	**Study Intervention**	**Number of Participants**	**Group Number**
7	Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age)	450	G7
8	Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age)	150	G8
9	BNT162b2 OMI 60 µg (participants 18 to 55 years of age)	300	G9

Abbreviation: IRC = internal review committee.

a. Sentinel cohorts will be sponsor open-label.

b. Participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required.

c. If the IRC's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2 and BNT162b2 OMI (25 µg each).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Safety Endpoints

The primary safety endpoints are as follows:

- Local reactions (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination
- Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after the study vaccination
- AEs from the study vaccination through 1 month after the study vaccination
- SAEs from the study vaccination through 6 months after the study vaccination
- Troponin I level at before and 3 days after study vaccination (sentinel cohort 18-55 years of age only)

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling and pain at the injection site, within 7 days after vaccination. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 5 defines the algorithm to derive the presence of a reaction (yes or no) during the interval within 7 days after the study vaccination.

Table 5. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for the Study Vaccination

Variable	Yes (1)	No (0)
Presence of each local reaction on any day	Participant reports the reaction as "yes" on any day (within 7 days after vaccination).	Participant reports the reaction as "no" on all 7 days (after vaccination) or as a combination of "no" and missing on all 7 days (after vaccination).
Presence of any local reaction on any day	Participant reports any local reaction as "yes" on any day (within 7 days after vaccination).	For all 3 local reactions, participant reports "no" on all 7 days (after vaccination) or a combination of "no" and missing on all 7 days (after vaccination).

Note: Missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 6. 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 mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Local Reaction Grading Scale

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
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

Table 6. Local Reaction Grading Scale

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
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

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale.

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.

For each local reaction after the study vaccination, the maximum severity grade will be derived for the e-diary collection period (within 7 days after the study vaccination) as follows:

Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination among the severity grades reported for that local reaction in the e-diary.

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive. Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasts 7 days or less, or the day the reaction ends if it persists beyond the end of the reactogenicity e-diary period following vaccination (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting the reaction with any severity after vaccination.

For the onset day of each local reaction, if participants report a change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after the study vaccination. The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 7.

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.

Table 7. Systemic Event Grading Scale

Systemic Event	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.

During the 7 days following the study vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as an AE rather than as systemic events in the reactogenicity e-diary.

Potential COVID-19 symptoms that do not overlap with systemic events should be reported as AEs as per protocol Section 8.3.

Oral temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period (7 days after the study vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperatures will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius first for reporting. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 8.

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.

Table 8. Scale for Fever

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

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will also be recorded in the reactogenicity e-diary daily during the reporting period (7 days after the study vaccination). For the use of antipyretic medication within 7 days after the study vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1 where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (7 days after the study vaccination)
- Presence (yes or no) of use of antipyretic medication on any day (within 7 days after the study vaccination)

- Duration (first to last day reported) of use of antipyretic medication
- Onset day of use of antipyretic medication

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after the study vaccination. In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF. AEs will be categorized according to MedDRA terms. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

The primary safety endpoint "AEs from the study vaccination through 1 month after the study vaccination" and other AE endpoints will be summarized by system organ class and preferred term.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.3.8 of the protocol).

3.1.1.5. Serious Adverse Events

SAEs will also be collected from the time of informed consent through approximately 6 months after the study vaccination. SAEs will be categorized according to MedDRA terms.

The safety endpoint "SAEs from the study vaccination through 6 months after the study vaccination" will be summarized by system organ class and preferred term. Additionally, SAEs will be listed.

3.1.1.6. Troponin I Level

Troponin I level will be collected at screening before study vaccination and 3 days after study vaccination for sentinel cohort participants 18-55 years of age. Percentage of participants with elevated troponin I levels will be summarized.

3.1.2. Primary Immunogenicity Endpoints

- G3vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg (Group 3) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G4vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg (Group 4) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G5vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg (Group 5) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G6vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg (Group 6) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

3.2. Secondary Endpoint(s)

- G5vG1B: SARS-CoV-2 reference-strain–neutralizing titers after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg (Group 5) compared to after 1 dose of BNT162b2 at 30 µg (Group 1) given as a fourth dose in BNT162b2-experienced participants >55 years of age.

- G6vG1B: SARS-CoV-2 reference-strain–neutralizing titers after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg (Group 6) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G3vG1B: SARS-CoV-2 Omicron-neutralizing titers after 1 dose of BNT162b2 OMI at 30 µg (Group 3) compared to after 1 dose of BNT162b2 at 30 µg (Group 1) given as a fourth dose in BNT162b2-experienced participants >55 years of age.

- G4vG1B: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg (Group 4) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G5vG1C: SARS-CoV-2 Omicron-neutralizing titers after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg (Group 5) compared to after 1 dose of BNT162b2 at 30 µg (Group 1) given as a fourth dose in BNT162b2-experienced participants >55 years of age.

- G6vG1C: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg (Group 6) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

3.3. Other Endpoint(s)

3.3.1. Exploratory Endpoints

- SARS-CoV-2 Omicron-neutralizing titers at each time point
- SARS-CoV-2 reference-strain–neutralizing titers at each time point
- SARS-CoV-2–neutralizing titers for the reference strain and VOCs in sentinel cohorts
- SARS-CoV-2–neutralizing titers for any VOCs not already specified
- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- Cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group

3.4. Baseline Variables

Measurements or samples collected prior to the study vaccination are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables will be collected including date of birth, sex (male or female), race (Black/African American, American Indian, or Alaskan native, Asian, Native Hawaiian, or other Pacific Islander, White, multiracial, and not reported), ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported), and BMI. In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the time of the study vaccination (in years) will be derived based on the participant's birthday. For example, if the study vaccination day is 1 day before the participant's 60th birthday, the participant is considered to be 59 years old.

Medical history will be collected and categorized according to the current version (at the time of reporting) of MedDRA.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant at Visit 601, a physical examination will be performed and any findings will be recorded in the source documents and, if clinically significant, on the medical history CRF.

3.4.1.1. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all the items on the e-diary for all 7 days after vaccination, the e-diary will be considered not transmitted.

3.4.1.2. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment until 28 days following administration of the study intervention.
- Prohibited medications listed in the protocol, Section 6.8.1, will be recorded to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- Prior and concomitant vaccines and concomitant medications will be coded using the WHO Drug Dictionary.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, SAEs and Troponin I level have been described above in the Primary Safety Endpoints section (Section 3.1.1).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in the table below. Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Table 9. Analysis Sets Description

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.

Table 9. Analysis Sets Description

Population	Description
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

Important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. 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.

The sponsor will be unblinded to the study intervention allocation for the sentinel cohorts. For the expanded-enrollment part of the study, the majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to the study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 10.11.6.2.2. The timing for statistical analysis is specified in Section 7.3.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

Superiority and Noninferiority of Omicron Immune Responses

The primary immunogenicity objective is to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti–Omicron immune response induced by a dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti–Omicron immune response elicited by a dose of BNT162b2 at 30 µg given as the fourth dose in BNT162b2-experienced participants >55 years of age. Each primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(1) corresponds to 1-fold superiority criterion and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 (30 µg or 60 µg) given as the fourth dose;

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 at 30 µg given as the fourth dose (Group 1).

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to Omicron strain at 1 month after 1 dose of BNT162b2 OMI or bivalent BNT162b2 and BNT162b2 OMI given as a fourth dose;

- p_2 is the percentage of participants with seroresponse to Omicron strain at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose (Group 1).

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Superiority will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

The secondary objectives of "super" superiority will be evaluated using a 1.5-fold margin for GMR. "Super" superiority for GMR will be established if the lower limit of the 2-sided 95% CI for the GMR is greater than 1.5.

Noninferiority of Reference Strain Immune Responses

The noninferiority immunogenicity objectives on reference strain immune responses are to assess the noninferiority of the reference strain immune response induced by a dose of bivalent BNT162b2 and BNT162b2 (30 µg or 60 µg) relative to the reference strain immune response elicited by a dose of BNT162b2 at 30 µg given as the fourth dose in BNT162b2-experienced participants >55 years of age. Each noninferiority objective will be evaluated by the following 2 hypotheses:

- The null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

- $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose (Group 5 or 6);

- $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured 1 month after 1 dose of BNT162b2 at 30 µg given as the fourth dose (Group 1).

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

5.1.2. Multiplicity Adjustment

The primary and secondary immunogenicity objectives will be assessed using the expanded-enrollment cohort.

The primary and secondary immunogenicity objectives will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G4vG1A (OMI-60) → G6vG1A (Bivalent-60) → G5vG1A (Bivalent-30) →
- Noninferiority in GMR for reference strain response: G6vG1B (Bivalent-60) → G5vG1B (Bivalent-30) →
- "Super" superiority in GMR for Omicron response: G4vG1B (OMI-60) →G6vG1C (Bivalent-60) → G5vG1C (Bivalent-30) →
- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G3vG1A (OMI-30) → G3vG1B (OMI-30)

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference will be assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled.

5.2. General Methods

All analyses will be performed separately for each age group (18-55 years of age, >55 years of age) unless otherwise specified.

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the levels of 95% unless specified otherwise.

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

As sensitivity approach, the difference in seroresponse rate between 2 vaccine groups and the associated 95% CI may be calculated using Miettinen and Nurminen method with baseline assay result category strata (<median, ≥median).

5.2.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Mean Titers

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

5.2.2.2. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios Between-Group Comparison

Unadjusted

For comparison of immune response between 2 vaccine groups, the GMR will be calculated as the mean of the difference of logarithmically transformed assay results between the two groups and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

Model-Based

As sensitivity approach, the GMR and associated 95% CI may be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of baseline assay results (log scale) and vaccine group.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the study vaccination date(s) from the same participant, following the Pfizer standard for handling incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

Missing serology 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; missing values will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- Reporting results: Descriptive statistics for each and any local reaction after the study vaccination in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplemental Analyses

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population as above, and appropriate analysis methodology and reporting results:

- Duration (days) of each local reaction after the study vaccination.

- Onset day of each local reaction after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for dose by vaccine group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after the study vaccination will be plotted for dose by vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimands: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after the study vaccination (Section 2.2).

- Analysis set: Safety population (Section 4).

- Analysis time point: Up to 7 days after the study vaccination.

- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; missing values will not be imputed. Confirmed e-diary errors will be excluded from the analysis.

- Reporting results: Descriptive statistics for each systemic event after the study vaccination in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analyses

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after the study vaccination.

- Onset day of each systemic event after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for the dose by vaccine group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the study vaccination through 1 month after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 1 month after the study vaccination for sentinel and expanded cohort.
- Analysis methodology: Descriptive statistics (Section 5.2.1 and Section 3.1.1.4).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of AEs within 1 month after the study vaccination will be provided for each vaccine group.

6.1.1.3.2. Supplemental Analyses

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.3.8 of the protocol) will also be summarized by vaccine group.

AEs from the study vaccination through 7 days after the study vaccination will be summarized similarly for IRC and at corresponding planned analysis timing described in Section 7.3.

All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be in the listing.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from the study vaccination through 6 months after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 6 months after the study vaccination for both sentinel and expanded cohorts.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the study vaccination through 6 months after the study vaccination will be provided for each vaccine group.
- Supplemental Analyses
- SAEs from the study vaccination through 7 days after the study vaccination will be summarized similarly for the IRC and at corresponding planned analysis timing described in Section 7.3.

6.1.1.5. Troponin I Level

6.1.1.5.1. Main Analysis

- Estimand: Percentage of participants with elevated troponin I level.
- Analysis set: Safety population of sentinel 18- to 55-year age cohort (Section 4).
- Analysis time point: Before the study vaccination and 3 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed (Section 5.3).
- Reporting results: Counts, percentages of participants with elevated troponin I level before study vaccination and 3 days after the study vaccination, and the associated Clopper-Pearson 95% CIs.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Main Analysis

Each primary immunogenicity objective involves 2 hypotheses based on GMR and difference of seroresponse rates.

For Superiority Hypothesis Test based on GMR of Omicron-Neutralizing Titer on G3vG1A, G4vG1A, G5vG1A, and G6vG1A:

- Estimands: GMRs of Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI 30 µg (Group 3), BNT162b2 OMI 60 µg (Group 4), bivalent BNT162b2 and BNT162b2 OMI 30 µg (Group 5), or bivalent BNT162b2 and BNT162b2 OMI 60 µg (Group 6) to those at 1 month after 1 dose of BNT162b2 30 µg given as a fourth dose (Group 1)

- Analysis set: Evaluable immunogenicity population, and all-available immunogenicity population (as applicable) of >55 years of age (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: GMRs and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.3.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.

- Reporting results: GMR and the associated 2-sided 95% CI will be provided.

For Noninferiority Hypothesis Tests on Seroresponse Rate of G3vG1A, G4vG1A, G5vG1A, and G6vG1A:

- Estimands: The difference in percentages of participants with seroresponse to Omicron strain at 1 month after study vaccination.

- Analysis set: Evaluable immunogenicity population and all-available immunogenicity population (as applicable) of >55 years of age (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: The percentages of participants with seroresponse for each group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (Section 5.2.1).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.

- Reporting results: Counts, percentages of participants with seroresponse in each group, the difference in percentages between groups, and the associated 2-sided 95% CI will be provided.

6.1.2.2. Sensitivity Analysis

GMRs and the associated 2-sided 95% CI, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs may be estimated using the sensitivity analysis approach specified in Section 5.2 (regression model-based estimate for GMR and stratified Miettinen and Nurminen estimate for difference in seroresponse rate).

6.1.3. Secondary Analysis

6.1.3.1. Main Analysis

For Noninferiority Hypothesis Tests of Reference-Strain–Neutralizing Titers on G5vG1B and G6vG1B:

- Estimands: GMRs of reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI 30 µg (Group 5), or bivalent BNT162b2 and BNT162b2 OMI 60 µg (Group 6) to those at 1 month after 1 dose of BNT162b2 30 µg given as a fourth dose (Group 1).

- Analysis set: Evaluable immunogenicity population, and all-available immunogenicity population (as applicable) >55 years of age (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: GMRs and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.3.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.

- Reporting results: GMR and the associated 2-sided 95% CI will be provided.

For "Super" Superiority Hypothesis Tests of Seroresponse Rate on G3vG1B, G4vG1B, G5vG1C, and G6vG1C:

- Estimands: GMRs of Omicron-neutralizing titers at 1 month 1 dose of BNT162b2 OMI 30 µg (Group 3), BNT162b2 OMI 60 µg (Group 4), bivalent BNT162b2 and BNT162b2 OMI 30 µg (Group 5), or bivalent BNT162b2 and BNT162b2 OMI 60 µg (Group 6) to those at 1 month after 1 dose of BNT162b2 30 µg given as a fourth dose (Group 1) after the study vaccination

- Analysis set: Evaluable immunogenicity population, and all-available immunogenicity population (as applicable) of >55 years of age (Section 4).

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: GMRs and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.3.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.

- Reporting results: GMR and the associated 2-sided 95% CI will be provided.

6.1.3.2. Sensitivity Analysis

GMRs and the associated 2-sided 95% CI, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs may be estimated using the sensitivity analysis approach specified in Section 5.2 (regression model-based estimate for GMR and stratified Miettinen and Nurminen estimate for difference in seroresponse rate).

6.1.4. Exploratory Immunogenicity Endpoints

6.1.4.1. SARS-CoV-2 Omicron- or Reference-Strain–Neutralizing Titers

- Estimands:

  1) GMTs of SARS-CoV-2 Omicron- and reference-strain–neutralizing titers at each time point for each vaccine group.

  2) GMFRs of SARS-CoV-2 Omicron- and reference-strain–neutralizing titers from before the study vaccination to subsequent time points for each vaccine group.

  3) Percentages of participants with seroresponse to Omicron or reference strain at each time point.

- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time point: Baseline and each subsequent time point after vaccination.
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.2.2.1. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.2.2.2. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group (Section 5.2.1).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from baseline (before the first study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

Figures:

- Empirical RCDCs will be provided for SARS-CoV-2 Omicron-strain and SARS-CoV-2 reference-strain–neutralizing titers at each time point for each vaccine group for sentinel and expanded cohort respectively.
- Bar charts of GMT and 95% CI of SARS-CoV-2 Omicron-strain and SARS-CoV-2 reference-strain–neutralizing titers will be plotted for each vaccine group for sentinel and expanded cohort, respectively.

6.1.4.2. SARS-CoV-2–Neutralizing Titers for the Reference Strain and VOCs for Sentinel Cohorts

- Estimands:
  1) GMTs of SARS-CoV-2–neutralizing titers for the reference strain and VOCs at each time point for each vaccine group.
  2) GMFRs of SARS-CoV-2–neutralizing titers for the reference strain and VOCs from before the study vaccination to each subsequent time point after vaccination for each vaccine group.
  3) Percentages of participants with seroresponse to reference strain and VOCs at each time point for each vaccine group.

- Analysis set: Evaluable immunogenicity population from sentinel cohorts.
- Analysis methodology: GMTs, GMFRs, and percentages of participants with seroresponse for sentinel cohorts, along with the associated 95% CIs, will be calculated using same method as described in Section 6.1.4.1.

6.1.4.3. SARS-CoV-2–Neutralizing Titers for Any VOCs Not Already Specified

- Estimands: GMTs for any VOCs not already specified, after any dose of BNT162b2 OMI or BNT162b2.
- Analyses: GMTs of SARS-CoV-2 VOC–neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs (Section 5.2.2.2) of SARS-CoV-2 VOC–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.

6.1.4.4. COVID-19 Cases

Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.

6.1.4.5. Cell-Mediated Immune Response

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron will be summarized at each time point for the subset of participants with PBMC samples collected in each vaccine group.

6.2. Subset Analyses

Subgroup analyses by sex, race, ethnicity, and baseline SARS-CoV-2 status will be performed on all primary safety and immunogenicity endpoints (as supplemental analyses). Subgroup analyses of immunogenicity endpoints by timing of previous dose of BNT162b2 may also be performed.

6.3. Baseline and Other Summaries and Analyses

6.3.1. Baseline Summaries

6.3.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination, sex, race, ethnicity, baseline SARS-CoV-2 status, and classification of BMI will be summarized using descriptive statistics for each vaccine group based on the safety population and the evaluable immunogenicity population. Timing of previous doses of BNT162b2 prior to enrollment will also be summarized for each vaccine group.

6.3.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of participants with at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group for the safety population.

6.3.2. Study Conduct and Participant Disposition

6.3.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the disposition summary. In addition, the numbers and percentages of participants who received vaccinations, who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately along with the reasons for exclusion, by vaccine group.

6.3.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for each time point by vaccine group.

6.3.2.3. Transmission of E-Diaries

The number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for each dose will be summarized according to the vaccine actually received.

The safety population will be used.

6.3.3. Study Intervention Exposure

6.3.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving the study intervention will be tabulated for each vaccine group and overall, for all randomized participants. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall.

A listing of participants showing the randomized vaccine and the vaccine actually received at the study vaccination will be presented.

6.3.3.2. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before the study vaccination will be listed. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated by vaccine group. Prohibited medications will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications will be provided. The safety population will be used.

6.4. Safety Summaries and Analyses

6.4.1. Adverse Events

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in the Primary Safety Endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analyses Timing

Statistical analyses will be carried out when the following data are available for each age group:

- Safety data through 1 month after study vaccination for each group in sentinel cohorts.
- Immunogenicity data through 1 month after study vaccination for each group in sentinel cohorts.
- Safety data through 1 month after study vaccination for each group in expanded-enrollment cohort.
- Immunogenicity data through 1 month after study vaccination for each group in expanded-enrollment cohort.
- Complete safety and immunogenicity analysis approximately 6 months after study vaccination for each group in sentinel or expanded-enrollment cohorts.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses for the expanded-enrollment cohort conducted while the study is ongoing will be performed by an unblinded team.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4): 404–13.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BLQ	below limit of quantitation
BMI	body mass index
BNT162b2 OMI	BNT162b2 OMICRON (B.1.1.529)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IRC	independent review committee
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
OMI	Omicron
PA	protocol amendment
PBMC	peripheral blood mononuclear cell
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VOC	variant of concern
WHO	World Health Organization