A PHASE 3, RANDOMIZED, OBSERVER-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF BNT162b2 WHEN COADMINISTERED WITH SEASONAL INACTIVATED INFLUENZA VACCINE (SIIV) IN ADULTS 18 THROUGH 64 YEARS OF AGE

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
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Brief Title: Safety and Immunogenicity of BNT162b2 Coadministered With SIIV in Adults 18 Through 64 Years

[redacted]

Document History

Document	Version Date
Amendment 2	09 March 2022
Amendment 1	22 December 2021
Original protocol	13 August 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.

Protocol Amendment Summary of Changes Table

Amendment 2 (09 March 2022)

Overall Rationale for the Amendment: Given the rapid and early COVID-19 vaccine third-dose (booster) rollout in southern hemisphere countries, the pool of potential study participants 18 through 64 years of age eligible to receive a third dose (booster) of BNT162b2 as part of this study will be significantly reduced. Also, it is possible that additional doses of BNT162b2 are required to improve protection against emerging variants; therefore, the protocol has been amended to assess coadministration of SIIV with a fourth dose (booster) of BNT162b2.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 (Synopsis), Section 1.2 (Schema), Section 2 (Introduction), Section 4.3 (Justification for Dose), Section 5.1 (Inclusion Criteria)	Updated the study design to replace the third dose (booster) of BNT162b2 with a fourth dose (booster) of BNT162b2. Revised the eligibility criterion to indicate that participants with 3 (rather than 2) prior doses of BNT162b2 would be included in this study. Added relevant data from publications and background information within the appropriate sections.	To increase the eligible population and evaluate a fourth dose (booster)	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 5.2 (Exclusion Criteria), Section 7.1 (Discontinuation of Study Intervention), Section 9.2 (Analysis Sets)	Modified exclusion criterion 5, excluding those participants who had a positive SARS-CoV-2 test result within 28 days prior to Visit 1. Associated sections were modified to reflect and align with modification of exclusion criterion 5.	To increase the eligible population and better reflect the real-world situation	Substantial
Section 1.1 (Synopsis), Section 4.1 (Overall Design), Section 5.5 (Criteria for Temporarily Delaying Enrollment/ Randomization/ Administration of Study Intervention), Section 9.3.1.2.1 (Geometric Mean Ratios)	Removed stratification on timing of the second dose of BNT162b2 prior to Visit 1 (Day 1) and added stratification by history of prior positive SARS-CoV-2 test result (with history and without history). Clarified that a positive SARS-CoV-2 test (rapid antigen or NAAT) within 28 days will result in temporary delay of study intervention administration.	To ensure comparable populations within each group	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 9.3.2 (Primary Endoint(s)/Estimand(s) Analysis)	Updated the linear regression model for the primary BNT162b2 immunogenicity endpoint to include evidence of SARS-CoV-2 infection as one of the factors (removing timing from the second dose at Visit 1).	To remain consistent with the change of study design and the consideration of current possible high infection rate	Nonsubstantial
Section 8.3.8 (Adverse Events of Special Interest), Section 8.9.1 (Visit 1 – Vaccination 1 (Day 1)	Added confirmed COVID-19 diagnosis or positive SARS-CoV-2 test result (by NAAT or rapid antigen test) as an AESI. Clarified that any history of COVID-19 diagnosis or prior positive SARS-CoV-2 test result by NAAT or rapid antigen test should be obtained as part of medical history at Visit 1.	To ensure consistent reporting for analysis	Nonsubstantial
Section 5.3.1 (Contraception)	Updated from "highly" to "acceptable" effective contraception.	To align with wording in Section 10.4	Nonsubstantial
Section 1.3 (Schedule of Activities), Section 8.9.2 (Visit 3 – [Follow-Up After Vaccination 2 – 28 to 42 Days After Vaccination 2])	Clarified that study intervention container allocation is obtained at Visit 1 and Visit 2.	Procedure clarification	Nonsubstantial

[redacted]

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 6.8.1 (Prohibited During the Study)	Clarified that receipt of any nonstudy influenza vaccine during study participation is prohibited.	Administrative clarification	Nonsubstantial
Section 10.1.3 (Informed Consent Process), Section 10.3.4 (Reporting of SAEs), Section 10.4 (Appendix 4: Contraceptive and Barrier Guidance)	Added minor details to clarify associated sections.	Administrative clarifications	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Safety and Immunogenicity of BNT162b2 Coadministered With SIIV in Adults 18 Through 64 Years

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 a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally at high speed.

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.

The Pfizer-BioNTech COVID-19 vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced a minimum of 21 days apart at a dose of 30 µg each, with the third dose (booster) being recommended at least 3 months after the second dose.

Like other COVID-19 vaccines recently developed, the long-term persistence of immunity and efficacy of BNT162b2 has yet to be studied. 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 the evaluation of booster doses to overcome waning immunity and/or the development of modified vaccines.

Annual seasonal influenza vaccination is recommended in a number of countries around the world to prevent influenza in adults ≥18 years of age, particularly adults with risk factors for increased influenza morbidity and mortality, such as older adults and those with chronic medical conditions. Currently, BNT162b2 is recommended for vaccination of adults to prevent COVID-19 caused by SARS-CoV-2, and several countries have implemented booster programs for adults ≥18 years of age. Since the recommendations for COVID-19 and influenza vaccination have considerable overlap, it is possible that both vaccines may need to be administered at the same time.

The SARS-CoV-2 variant Omicron (B.1.1.529 and BA lineages), also known as Omicron, is currently the dominant variant in many countries and, within the US, is responsible for 100% of sequenced COVID-19 cases as of the week ending 19 February 2022. Early data noted that the vaccine effectiveness against hospitalization is 90% (95% CI: 80%-94%) for Omicron after 3 doses of any mRNA 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 fourth dose (booster) may improve protection, with increased longevity of an immune response, provided it has a tolerable safety profile.

Israel has implemented a fourth dose (booster) of BNT162b2 in healthcare workers, adults 60 years of age and older, and immunocompromised people who have received 3 prior doses of BNT162b2. Preliminary data show up to 2 times higher protection against symptomatic disease and up to 3 times higher protection against severe disease compared to those who have received 3 doses of BNT162b2.

The purpose of this study is to assess the safety and immunogenicity of a fourth dose (booster) of BNT162b2 administered concomitantly with SIIV or 1 month apart in participants who have had 3 previous doses of BNT162b2 as per recommended dosing schedule.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety Objective:	**Primary Safety Estimands:**	**Primary Safety Endpoints:**
To describe the safety profile of BNT162b2 when coadministered with SIIV	In participants receiving 1 dose of BNT162b2 and SIIV or saline and having safety follow-up after vaccination from each vaccine group, the percentage of participants reporting: • Local reactions within 7 days after each vaccination • Systemic events within 7 days after each vaccination • AEs within 1 month after each vaccination • SAEs from the first vaccination up to 1 month after the last vaccination	• Local reactions (redness, swelling, and pain at the injection site) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary BNT162b2 Immunogenicity Objective:	**Primary BNT162b2 Immunogenicity Estimand:**	**Primary BNT162b2 Immunogenicity Endpoint:**
To demonstrate that the immune responses elicited by BNT162b2 when coadministered with SIIV (BNT162b2+SIIV) are noninferior to those elicited by BNT162b2 when administered alone	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 in the coadministration group to the IgG levels 1 month after vaccination with BNT162b2 in the separate-administration group	• Full-length S-binding IgG levels
Primary SIIV Immunogenicity Objective:	**Primary SIIV Immunogenicity Estimand:**	**Primary SIIV Immunogenicity Endpoints:**
To demonstrate that the immune responses elicited by SIIV when coadministered with BNT162b2 (BNT162b2+SIIV) are noninferior to those elicited by SIIV when administered alone	In evaluable participants: • GMR of the strain-specific HAI (or H3N2-neutralizing antibody) titers 1 month after vaccination with SIIV in the coadministration group to the corresponding HAI (or H3N2-neutralizing antibody) titers in the separate-administration group	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)
Secondary BNT162b2 Immunogenicity Objective:	**Secondary BNT162b2 Immunogenicity Estimands:**	**Secondary BNT162b2 Immunogenicity Endpoints:**
To describe the immune responses elicited by BNT162b2 when coadministered with SIIV or administered alone	In evaluable participants from each vaccine group: • GMCs/GMTs before vaccination and 1 month after vaccination with BNT162b2 • GMFR from before vaccination to 1 month after vaccination with BNT162b2	• Full-length S-binding IgG levels • SARS-CoV-2–neutralizing titers (for a subset of approximately 200 participants)

Secondary SIIV Immunogenicity Objective:	**Secondary SIIV Immunogenicity Estimands:**	**Secondary SIIV Immunogenicity Endpoints:**
To describe the immune responses elicited by SIIV when coadministered with BNT162b2 or administered alone	In evaluable participants from each vaccine group: • GMTs before vaccination and 1 month after vaccination with SIIV • GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination with SIIV	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)
Exploratory Immunogenicity Objective:	**Exploratory Immunogenicity Estimands**	**Exploratory Immunogenicity Endpoints:**
To further describe the immune responses elicited by SIIV when coadministered with BNT162b2 or administered alone	In evaluable participants from each vaccine group: • The percentage of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV • The percentage of participants with strain-specific HAI seroconversion 1 month after vaccination with SIIV • The percentage of participants with H3N2 neutralization seroprotection 1 month after vaccination with SIIV • The percentage of participants with H3N2 neutralization seroconversion 1 month after vaccination with SIIV	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)

Overall Design

This Phase 3, multicenter, randomized, observer-blind study, with a 2-arm parallel design, will be conducted at investigator sites in the southern hemisphere. The purpose of this study is to assess the safety and immunogenicity of BNT162b2 and SIIV given together compared to the vaccines given 1 month apart. Approximately 1126 participants will be randomized at a ratio of 1:1 into the coadministration group and the separate-administration group stratified by age group (18-49 years and 50-64 years), and by history of positive SARS-CoV-2 test result by NAAT or rapid antigen test prior to randomization (with prior history of SARS-CoV-2 and without prior history of SARS-CoV-2). A single lot of SIIV is proposed for the study, and ideally this SIIV would be recommended for use in adults 18 through 64 years of age; however, ultimately the SIIV used may be determined by supply availability.

Local reactions (redness, swelling, and pain at the injection site) occurring at the BNT162b2 or saline injection site within 7 days and systemic events (fever, headache, fatigue/tiredness, chills, vomiting, diarrhea, new or worsening muscle pain, and new or worsening joint pain) occurring within 7 days after each vaccination (Visit 1 and Visit 2) will be prompted for and collected daily by the participant in an e-diary device or application. Use of antipyretic/pain

medications will also be prompted for and collected daily in the reactogenicity e-diary for 7 days after each vaccination.

AEs and SAEs will be collected from the signing of informed consent through Visit 3 (approximately 1 month after Vaccination 2).

To assess immunogenicity, approximately 30 mL of blood will be collected at 3 study visits from all participants: at Visit 1 (prior to Vaccination 1); at Visit 2 (prior to Vaccination 2); and at Visit 3 (1 month after Visit 2).

Number of Participants

Approximately 1126 participants will be randomized for a total of approximately 900 evaluable participants (assuming a 20% nonevaluable rate).

Intervention Groups and Duration

Each participant will participate in the study for approximately 2 months. Based on an estimated 1- to 2-month enrollment, the study duration will be approximately 3 to 4 months. All participants will receive BNT162b2, SIIV, and saline via intramuscular injection.

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 primary immunogenicity objectives will be evaluated by formal hypothesis tests for noninferiority of coadministration of BNT162b2 and SIIV (coadministration group) to administration of SIIV followed by BNT162b2 1 month later (separate-administration group), based on full-length S-binding IgG levels 1 month after vaccination with BNT162b2 and strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) 1 month after vaccination with SIIV. Noninferiority of the coadministration group to the separate-administration group will be declared for full-length S-binding IgG levels or an influenza strain if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to separate-administration group) is >0.67. The primary immunogenicity objectives of the study will be achieved if noninferiority is met for the full-length S-binding IgG levels and for each of the influenza strains.

The other immunogenicity objectives will be evaluated descriptively by GMCs/GMTs before vaccination and at 1 month after vaccination, GMFRs from before vaccination to 1 month after vaccination, percentage of participants with strain-specific HAI (or H3N2 neutralization) seroconversion and strain-specific HAI titers ≥1:40 (or H3N2 neutralization seroprotection) 1 month after vaccination, and the associated 2-sided 95% CIs for full-length S-binding IgG levels and/or strain-specific HAI titers (or H3N2-neutralizing antibody titers).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs, and SAEs for each vaccine group. A 3-tier approach will be used to summarize AEs.

1.2. Schema

	Visit Number	**1**	**2**	**3**
	Visit Description	**Vaccination 1**	**Vaccination 2 (1 Month After Vaccination 1)**	**1-Month Follow-Up Visit**
Participants having received 3 prior doses of 30 µg BNT162b2 ≥90 days prior to Visit 1 randomization	Group 1 (563)	BNT162b2+ SIIV	Placebo	
	Group 2 (563)	Placebo+ SIIV	BNT162b2	
	Immunogenicity blood draw	30 mL	30 mL	30 mL

Abbreviation: SIIV = seasonal inactivated influenza vaccine.

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.

Visit Number	**1**	**2**	**3**
Visit Description	**Vaccination 1**	**Vaccination 2**	**Follow-Up After Vaccination 2**
Visit Window	**Day 1**	**28 to 42 Days After Vaccination 1**	**28 to 42 Days After Vaccination 2**
Obtain informed consent	X		
Assign participant number	X		
Obtain demography and medical history data	X		
Perform clinical assessment[a]	X		
Record BNT162b2 vaccine history	X		
Collect and record nonstudy vaccinations	X	X	X
Measure temperature (oral)	X	X	
Perform urine pregnancy test (if appropriate)	X	X	
Confirm use of contraceptives (if appropriate)	X	X	X
Collect prohibited medication use	X	X	X
Confirm eligibility	X	X	
Review temporary delay criteria	X	X	
Obtain randomization number	X		
Obtain study intervention container allocation using the IRT system	X	X	

Visit Number	1	2	3
Visit Description	**Vaccination 1**	**Vaccination 2**	**Follow-Up After Vaccination 2**
Visit Window	**Day 1**	**28 to 42 Days After Vaccination 1**	**28 to 42 Days After Vaccination 2**
For participants who are HIV-positive, record latest HIV viral load and CD4 count	X		X
Collect blood sample for immunogenicity assessment	30 mL	30 mL	30 mL
Administer study intervention	X	X	
Assess acute reactions for at least 30 minutes after study intervention administration	X	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	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)	X	X	
Review ongoing reactogenicity e-diary symptoms with participant and obtain stop dates		X	X
Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations.	X	X	
Collect AEs and SAEs	X	X	X
Request the participant return the e-diary or assist the participant to delete the application			X

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

a. Including, if indicated, a physical examination.

[redacted]

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 full marketing authorization, 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. 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 the evaluation of booster doses to overcome waning immunity and/or the development of modified vaccines.[5]

Annual seasonal influenza vaccination is recommended in many countries around the world to prevent influenza in adults ≥18 years of age, particularly adults with risk factors for increased influenza morbidity and mortality, such as older adults and those with chronic medical conditions.[6] Since the recommendations for COVID-19 and influenza vaccination have considerable overlap, it is possible that both vaccines may need to be administered at the same time.[7]

The SARS-CoV-2 variant Omicron (B.1.1.529 and BA lineages), also known as Omicron, is currently the dominant variant in many countries and, within the US, is responsible for 100% of sequenced COVID-19 cases as of the week ending 19 February 2022.[8,9] Early data noted that the vaccine effectiveness against hospitalization is 90% (95% CI: 80%-94%) for Omicron after 3 doses of any mRNA vaccine.[10] However, even with 3 vaccine doses, neutralization against the Omicron variant was lower (by a factor of 4) than that against the Delta variant.[11] The addition of a fourth dose (booster) may improve protection, with increased longevity of an immune response, provided it has a tolerable safety profile.

Israel has implemented a fourth dose (booster) of BNT162b2 in healthcare workers, adults 60 years of age and older, and immunocompromised people who have received 3 prior doses of BNT162b2. Preliminary data show up to 2 times higher protection against symptomatic disease and up to 3 times higher protection against severe disease compared to those who have received 3 doses of BNT162b2.[12]

The purpose of this study is to assess the safety and immunogenicity of a fourth dose (booster) of BNT162b2 administered concomitantly with SIIV or 1 month apart in participants who had 3 previous doses of BNT162b2 as per the recommended dosing schedule.

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. 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.[13,14] 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.[15] 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.[16]

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 full marketing, temporary, or emergency authorizations.[17]

The Pfizer-BioNTech COVID-19 vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced a minimum of 21 days apart at a dose of 30 µg each, with the third dose (booster) being recommended at least 3 months after the second dose.[18,19]

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.[20] 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.[21]

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.[22] 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.[21]

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.[21]

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.[23] 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.[24] 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.[25] 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.[26,27]

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.[28]

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with several SARS-CoV-2 vaccines now in use under full marketing authorizations, conditional 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 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%).[21] 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 participants ≥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.[21]

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.[21]

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 of 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.[22]

The tolerability profile of fourth doses of BNT162b2 has yet to be described in peer-reviewed publications; however, fourth doses have been administered in some countries.[12] Based on preliminary data published, it is expected that the potential benefits outweigh the risks.

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 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.

The SRSD for the SIIV is the product information for the country where the vaccine was procured.

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.[21]	• Local reactions and systemic events will be recorded in an e-diary. • 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: anaphylaxis, other hypersensitivity reactions (eg, rash, pruritus, urticaria, angioedema), pain in extremity (injected arm), vomiting, and diarrhea. Please refer to the latest version of the IB for the most recent safety information.	Data available from Study C4591001 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.[21] 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 this table.	• Collection of AEs from signing of the ICD through 1 month after the booster vaccination. • Collection of SAEs from signing of the ICD through 1 month 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 AEs. • 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.

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 8.11.
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. In addition, local travel and movement restrictions could impact study visit conduct and protocol compliance.	• Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy and to mitigate the impact of local travel restrictions. • Monitoring for cases of COVID-19 developing during the study, which will be reported as AEs.
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 fourth dose (booster) 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
- Receipt of a licensed influenza vaccine

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risks to participants participating in the study, the potential risks identified in association with BNT162b2 are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary Safety Objective:	**Primary Safety Estimands:**	**Primary Safety Endpoints:**
To describe the safety profile of BNT162b2 when coadministered with SIIV	In participants receiving 1 dose of BNT162b2 and SIIV or saline and having safety follow-up after vaccination from each vaccine group, the percentage of participants reporting: • Local reactions within 7 days after each vaccination • Systemic events within 7 days after each vaccination • AEs within 1 month after each vaccination • SAEs from the first vaccination up to 1 month after the last vaccination	• Local reactions (redness, swelling, and pain at the injection site) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary BNT162b2 Immunogenicity Objective:	**Primary BNT162b2 Immunogenicity Estimand:**	**Primary BNT162b2 Immunogenicity Endpoint:**
To demonstrate that the immune responses elicited by BNT162b2 when coadministered with SIIV (BNT162b2+SIIV) are noninferior to those elicited by BNT162b2 when administered alone	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 in the coadministration group to the IgG levels 1 month after vaccination with BNT162b2 in the separate-administration group	• Full-length S-binding IgG levels

Primary SIIV Immunogenicity Objective:	**Primary SIIV Immunogenicity Estimand:**	**Primary SIIV Immunogenicity Endpoints:**
To demonstrate that the immune responses elicited by SIIV when coadministered with BNT162b2 (BNT162b2+SIIV) are noninferior to those elicited by SIIV when administered alone	In evaluable participants: • GMR of the strain-specific HAI (or H3N2-neutralizing antibody) titers 1 month after vaccination with SIIV in the coadministration group to the corresponding HAI (or H3N2-neutralizing antibody) titers in the separate-administration group	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)
Secondary BNT162b2 Immunogenicity Objective:	**Secondary BNT162b2 Immunogenicity Estimands:**	**Secondary BNT162b2 Immunogenicity Endpoints:**
To describe the immune responses elicited by BNT162b2 when coadministered with SIIV or administered alone	In evaluable participants from each vaccine group: • GMCs/GMTs at before vaccination and 1 month after vaccination with BNT162b2 • GMFR from before vaccination to 1 month after vaccination with BNT162b2	• Full-length S-binding IgG levels • SARS-CoV-2–neutralizing titers (for a subset of approximately 200 participants)
Secondary SIIV Immunogenicity Objective:	**Secondary SIIV Immunogenicity Estimands:**	**Secondary SIIV Immunogenicity Endpoints:**
To describe the immune responses elicited by SIIV when coadministered with BNT162b2 or administered alone	In evaluable participants from each vaccine group: • GMTs before vaccination and 1 month after vaccination with SIIV • GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination with SIIV	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)
Exploratory Immunogenicity Objective:	**Exploratory Immunogenicity Estimands**	**Exploratory Immunogenicity Endpoints:**
To further describe the immune responses elicited by SIIV when coadministered with BNT162b2 or administered alone	In evaluable participants from each vaccine group: • The percentage of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV • The percentage of participants with strain-specific HAI seroconversion 1 month after vaccination with SIIV • The percentage of participants with H3N2 neutralization seroprotection 1 month after vaccination with SIIV • The percentages of participants with H3N2 neutralization seroconversion 1 month after vaccination with SIIV	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, randomized, observer-blind study with a 2-arm parallel design will be conducted at investigator sites in the southern hemisphere. The purpose of this study is to assess the safety and immunogenicity of BNT162b2 and SIIV given together compared to the vaccines given 1 month apart. Approximately 1126 participants will be randomized at a ratio of 1:1 into the coadministration group and the separate-administration group stratified by age group (18-49 years and 50-64 years) and by history of positive SARS-CoV-2 test result by NAAT or rapid antigen test prior to randomization (with prior history of SARS-CoV-2 and without prior history of SARS-CoV-2). A single lot of SIIV is proposed for the study, and ideally this SIIV would be recommended for use in adults 18 through 64 years of age; however, ultimately the SIIV used may be determined by supply availability.

Local reactions (redness, swelling, and pain at the injection site) occurring at the BNT162b2 or saline injection site within 7 days and systemic events (fever, headache, fatigue/tiredness, chills, vomiting, diarrhea, new or worsening muscle pain, and new or worsening joint pain) occurring within 7 days after each vaccination (Visit 1 and Visit 2) will be prompted for and collected daily by the participant in an e-diary device or application. Use of antipyretic/pain medications will also be prompted for and collected daily in the reactogenicity e-diary for 7 days after each vaccination.

AEs will be collected from the signing of informed consent through Visit 3 (approximately 1 month after Vaccination 2). SAEs will be collected from the signing of informed consent through Visit 3.

To assess immunogenicity, approximately 30 mL of blood will be collected from all participants at 3 study visits: at Visit 1 (prior to Vaccination 1); at Visit 2 (prior to Vaccination 2); and at Visit 3 (1 month after Visit 2).

Each participant will participate in the study for approximately 2 months. Based on an estimated 1- to 2-month enrollment, the study duration will be approximately 3 to 4 months. All participants will receive BNT162b2, SIIV, and saline via intramuscular injection.

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for BNT162b2; therefore, the use of a highly effective method of contraception is required (see Appendix 4). However, there is no suspicion of human teratogenicity based on the intended pharmacology of the compound.

4.3. Justification for Dose

Based on data from the Phase 1 component of Study 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 for use and authorized for temporary or emergency use in multiple countries worldwide, and has been recommended as a third dose (booster). The same dose will therefore be used in this study as a fourth dose (booster).

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.

A participant is considered to have completed the study if he/she has completed all phases of the 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 following criteria apply:

Age and Sex:

1. Participants 18 through 64 years of age, inclusive, at the time of consent.

    - 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. Are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Adults determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study, including adults with preexisting stable disease, defined as disease not requiring significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of study intervention.

   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 Appendix 7, Section 10.7.

4. Have received 3 prior doses of 30 µg BNT162b2, with the third dose being at least 90 days before Visit 1 (Day 1). Documented confirmation of prior BNT162b2 receipt must be obtained prior to randomization.

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.

5.2. Exclusion Criteria

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

Medical Conditions:

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

2. Allergy to egg proteins (egg or egg products) or chicken proteins.

3. History of Guillain-Barré syndrome.

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

5. A positive SARS-CoV-2 test result (either by NAAT or rapid antigen test) within 28 days of Visit 1 (Day 1).

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

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

8. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

9. Vaccination with any influenza vaccine <6 months before study intervention administration, or planned receipt of any licensed or investigational nonstudy influenza vaccine during study participation.

10. 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 COPD, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

12. Receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration or planned receipt throughout the study.

13. Prior receipt of any COVID-19 vaccine other than BNT162b2 or receipt of more than 3 prior doses of BNT162b2.

Prior/Concurrent Clinical Study Experience:

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

Other Exclusions:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Section 10.4, 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 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 SAE.

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

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 (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration. This includes a positive SARS-CoV-2 test result (NAAT or rapid antigen test) within 28 days.

2. Receipt of any nonstudy vaccine within 28 days before study intervention administration.

3. Anticipated receipt of any nonstudy vaccine within 28 days after study intervention administration.

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

6. STUDY INTERVENTION(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

Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA – single-dose vial
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	30 µg (administered as a 0.3-mL dose)
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 per country requirement.

Additional Intervention Name	Saline Placebo
Type	Placebo
Dose Formulation	Normal saline (0.9% sodium chloride solution for injection) – single-dose vial
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 per country requirement.

6.1.1. Concomitant Vaccine

Licensed SIIV containing strains of influenza viruses that are antigenically like the annually recommended mammalian cell-produced or egg-produced strains will be supplied to the site and packaged as commercial supplies. Pfizer will provide this vaccine; however, with approval by the sponsor, a site may independently procure the study-specific SIIV rather than receive shipment of SIIV from the sponsor. SIIV will be shipped and stored as per the commercial package insert and commercial label. Administration of SIIV will be recorded in the CRF.

6.1.2. Administration

The vaccines and placebo will be administered by an **unblinded** third-party site staff member at Visit 1 and Visit 2.

Table 1. Vaccine Administration per Group

	Visit 1 – Vaccination 1	Visit 2 – Vaccination 2
Group 1 Left deltoid	0.3 mL of BNT162b2 injected intramuscularly	0.3 mL of saline injected intramuscularly
Group 1 Right deltoid	SIIV injected intramuscularly	N/A
Group 2 Left deltoid	0.3 mL of saline injected intramuscularly	0.3 mL of BNT162b2 injected intramuscularly
Group 2 Right deltoid	SIIV injected intramuscularly	N/A

Abbreviation: SIIV = seasonal inactivated influenza vaccine.

Standard vaccination practices must be observed, and the vaccine must not be injected into the blood vessels. Appropriate medication and other supportive measures for the 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 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 dispensing.

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in a blinded fashion to the participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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

6.3.2.1. Blinding of Site Personnel

In this observer-blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because 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.

6.3.2.2. Blinding of the Sponsor

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation until the analysis at the completion of the study. All laboratory testing personnel performing serology assays will remain blinded to the 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 statistician and programmer supporting interactions with, and analyses for, the DMC (see Section 10.1.5)

6.3.2.3. 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.

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 will be recorded in the source documents and recorded in the CRF. The blinded 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.

6.5. Dose Modification

Not applicable.

6.6. 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.

6.7. 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 through Visit 3.
- 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 the study intervention should be administered within 28 days before and 28 days after each study vaccination.
- Vaccination with any influenza vaccine within 6 months (182 days) before study intervention administration or receipt of any nonstudy influenza vaccine during study participation is prohibited.
- 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 (including monoclonal antibodies) 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

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

Medications and vaccines other than those described as prohibited in Section 6.8.1 required for treatment of preexisting conditions or acute illness are 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 are allowed to 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 of the inclusion criteria, or meeting 1 or more exclusion criteria*).

*A positive SARS-CoV-2 test result (either by NAAT or rapid antigen test) should not result in discontinuation of study intervention. If study intervention has been delayed per Section 5.5, the participant may be vaccinated once the condition(s) has/have resolved.

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 study intervention discontinuation and follow-up on any further evaluations that need to be completed. Participants who remain in the study for evaluation of safety will be contacted by telephone 1 month after their last study vaccination to record AEs as described in Section 8.3.

In the event of study intervention discontinuation, 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

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.

The total blood sampling volume for individual participants in this study is approximately 90 mL. The actual collection times of blood sampling may change. 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. Efficacy and/or Immunogenicity Assessments

Serum samples may be obtained for immunogenicity testing at the visits specified in the SoA.

The following assays will be performed:

- Full-length S-binding IgG assay.
- SARS-CoV-2 neutralization assay (reference strain and, CCI [redacted]).
- N-binding antibody assay to establish prior serological exposure to SARS-CoV-2: to be performed using samples collected at Visit 1 (baseline), Visit 2 (prior to Vaccination 2), and Visit 3.
- HAI titers to the influenza strains in the SIIV administered and H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained) will be determined on sera collected at Visits 1 and 2 (prior to and 1 month [28 to 42 days] after SIIV administration).

Sera and plasma remaining after completion of the planned immunologic assays from blood draws taken throughout the study may be used for additional vaccine and infectious disease-related research, including exploratory immunologic assays for further characterization of the immune responses to BNT162b2 and/or SIIV.

8.1.1. Biological Samples

Blood 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 Section 8.3.1 to Section 8.3.3.

8.2.2. Vital Signs

The participant's oral temperature will be measured prior to each vaccination.

8.2.3. 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 use of antipyretic medication for 7 days from the day of administration of the study intervention. The reactogenicity e-diary allows the recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

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

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.

8.2.3.1. 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.[29]

8.2.3.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the BNT162b2 or saline 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 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 as detailed in Appendix 3.

8.2.3.3. 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)[a]
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.

a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 systemic events will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Appendix 3.

8.2.3.4. 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 ≥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)

8.2.3.5. Antipyretic Medication

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

8.2.4. Clinical Safety Laboratory Assessments

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Section 8.11 for additional procedures for monitoring of potential myocarditis or pericarditis.

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3.

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 is 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 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 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

Not applicable.

8.3.8. Adverse Events of Special Interest

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 Section 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.

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 8.11 for additional procedures for monitoring of potential myocarditis or pericarditis.
- A confirmed COVID-19 diagnosis, or positive SARS-CoV-2 test result (by NAAT or rapid antigen test).

8.3.8.1. 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**.

8.3.9. 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

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.

8.9. Study Procedures

8.9.1. Visit 1 –Vaccination 1 (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. 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, including any history of COVID-19 diagnosis or prior positive SARS-CoV-2 test result by NAAT or rapid antigen test. 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.
- Record previous BNT162b2 vaccine history.
- 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 and record the participant's oral temperature (°C).
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.1.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication as described in Section 6.8.1.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Record AEs as described in Section 8.3.
- Obtain the participant's randomization number and study intervention container allocation using the IRT system.
- Collect a blood sample (approximately 30 mL) for immunogenicity testing, prior to vaccination.

[redacted]

- An unblinded site staff member will administer a single 0.3-mL injection of BNT162b2 vaccine or saline into the left deltoid muscle.
- An unblinded site staff member will administer a single 0.5-mL injection of SIIV into the right deltoid muscle.
- Blinded site staff will observe the participant for at least 30 minutes after administration of BNT162b2 or saline for any reactions. Record any AEs on the CRF and on the Vaccine SAE Reporting Form, as applicable.
- Issue the participant a measuring device to measure BNT162b2 vaccine or saline injection site reactions in the left deltoid muscle and a digital thermometer and provide instructions on their use.
- Explain the e-diary technologies available for this study (see Section 8.2.3), 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.
- 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 BNT162b2 vaccine or saline injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the BNT162b2 or saline injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant, 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.
- 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.

8.9.2. Visit 2 – Vaccination 2 – 28 to 42 Days After Visit 1

- Record AEs as described in Section 8.3.
- Ensure and document that the participant continues to be eligible for the study (see Section 7 for participant discontinuation/withdrawal) and that none of the temporary delay criteria are met.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication as described in Section 6.8.1.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 5.3.1.
- Review the participant's e-diary data. Collect stop dates of any e-diary events (local reactions or systemic events) ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF.
- Measure and record the participant's oral temperature (°C).
- Obtain the participant's study intervention container allocation using the IRT system.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments prior to vaccination.
- An unblinded site staff member will administer a single 0.3-mL injection of the BNT162b2 or saline into the left deltoid muscle.
- Blinded site staff will observe the participant for at least 30 minutes after administration of the BNT162b2 or saline for any reactions. Record any AEs on the CRF and on the Vaccine SAE Reporting Form, as applicable.
- Confirm that the e-diary is working and review instructions, if necessary. Ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination. Provide thermometer or measuring device, if needed.

- 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 BNT162b2 or saline injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the BNT162b2 or saline injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant, 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.
- 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.

8.9.3. Visit 3 – (Follow-Up After Vaccination 2 – 28 to 42 Days After 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 prohibited medication as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 5.3.1.

- 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 30 mL) for immunogenicity testing.
- Collect e-diary or assist the participant with deleting the application.
- 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.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

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

If a Grade 3 local reaction (Section 8.2.3.2), systemic event (Section 8.2.3.3), or fever Section 8.2.3.4) 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 8.2.3.2), systemic event (Section 8.2.3.3), or fever (Section 8.2.3.4) 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 classification.

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

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

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

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

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

- Measure oral temperature (°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 8.2.3.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.3.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.11. 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 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.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described 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. Statistical Hypothesis

9.1.1.1. Statistical Hypothesis for BNT162b2

The primary immunogenicity objective on immune response elicited by BNT162b2 will be evaluated by the following hypothesis:

$$H_{01}: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority, and $\ln(\mu_A)$ and $\ln(\mu_B)$ are the natural log of the geometric mean of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 for the coadministration group and the separate-administration group, respectively. Noninferiority will be declared if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to separate-administration group) is >0.67.

9.1.1.2. Statistical Hypothesis for SIIV

The primary immunogenicity objective on immune response elicited by SIIV will be evaluated by the following hypothesis:

$$H_{02}: \ln(\mu_C) - \ln(\mu_D) \leq \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority, and $\ln(\mu_C)$ and $\ln(\mu_D)$ are the natural log of the geometric mean of the strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) 1 month after vaccination with SIIV for the coadministration group and the separate-administration group, respectively. Noninferiority will be declared for an influenza strain if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to separate-administration group) is >0.67. The primary SIIV immunogenicity objective of the study will be achieved if the noninferiority is met for each of the influenza strains.

9.1.2. Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in the table in Section 3.

The estimands to evaluate the immunogenicity objectives will be based on the evaluable immunogenicity population (Section 9.2). These estimands estimate the vaccine effect in the hypothetical settings where participants follow the study schedules and protocol requirements as directed. The estimands address the objective of estimating the maximum potential difference between 2 vaccine groups of the target population, since the impact of noncompliance is likely to diminish the observed difference between the 2 compared groups. 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.

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

9.1.3. Multiplicity Adjustment

For the primary immunogenicity assessment of noninferiority of coadministration of BNT162b2 and SIIV to administration of SIIV followed by BNT162b2 1 month later, the hypotheses for the full-length S-binding IgG levels and for all the influenza strains in SIIV will be tested at a 1-sided alpha level of 0.025.

The primary immunogenicity objectives of the study will be achieved if noninferiority is met for the full-length S-binding IgG levels and for each of the influenza strains. Therefore, the type I error rate for the immunogenicity assessments is well controlled.

9.2. Analysis Sets

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

Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable BNT162b2 immunogenicity	All eligible randomized participants who receive all vaccinations at Visit 1 as randomized (coadministration group) or receive all vaccinations at Visit 1 and Visit 2 as randomized (separate-administration group), have at least 1 valid and determinate full-length S-binding IgG or SARS-CoV-2–neutralizing titer result from the blood sample collected within an appropriate window at Visit 2 (coadministration group) or at Visit 3 (separate-administration group), and have no other important protocol deviations as determined by the clinician.
Evaluable SIIV immunogenicity	All eligible randomized participants who receive all vaccinations at Visit 1 as randomized, have at least 1 valid and determinate HAI titer or H3N2-neutralizing antibody titer result from the blood sample collected within an appropriate window at Visit 2, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who have at least 1 valid and determinate immunogenicity result after receiving the study intervention.
Safety	All participants who receive any of the study intervention.

9.3. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.4. It 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 populations. Participants will be summarized by vaccine group according to the study intervention they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE start dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity populations. 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. Missing serology data will not be imputed.

9.3.1.1. Analysis 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 2-sided 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[30] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[31]

3-Tier Approach for AE Summary

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:

1. Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; there is no Tier 1 event identified for BNT162b2 at this stage.

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;

3. Tier 3 events are those that are neither Tier 1 nor Tier 2 events.

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, the 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, descriptive summary statistics for each vaccine group will be provided.

9.3.1.2. Analysis 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 Mean Ratios

Model-Based

As the primary approach, the GMRs and associated 95% CIs will be calculated by exponentiating the difference in LS means of the 2 vaccine groups and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with vaccine group, age group, and evidence of SARS-CoV-2 infection (through 1 month after BNT162b2 vaccination [yes or no]) as factors.

Unadjusted

The GMRs will be calculated as the difference in the means of logarithmically transformed assay results for the 2 groups and exponentiating the difference. The associated 2-sided 95% 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.

9.3.1.2.2. 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 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.

9.3.1.2.4. 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.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
BNT162b2 immunogenicity	**GMR of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 (at Visit 1) in the coadministration group to the IgG levels 1 month after vaccination with BNT162b2 (at Visit 2) in the separate-administration group** GMR and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 9.3.1.2.1. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. As the primary approach for the noninferiority assessment, a linear regression model that includes vaccine group, age group, and evidence of SARS-CoV-2 infection (through 1 month after BNT162b2 vaccination) will be used to calculate the adjusted GMR and 2-sided 95% CI. The unadjusted GMR and CI will also be calculated.
SIIV immunogenicity	**GMR of the strain-specific HAI (or H3N2-neutralizing antibody) titers 1 month after vaccination with SIIV in the coadministration group to the corresponding HAI (or H3N2-neutralizing antibody) titers in the separate-administration group** For each influenza strain, GMR and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 9.3.1.2.1. Noninferiority for a strain will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. The primary SIIV immunogenicity objective of the study will be achieved if the noninferiority is met for each of the influenza strains. As the primary approach for the noninferiority assessment, a linear regression model that includes vaccine group, age group, and evidence of SARS-CoV-2 infection (through 1 month after BNT162b2 vaccination) will be used to calculate the adjusted GMR and 2 sided 95% CI. The unadjusted GMR and CI will also be calculated.

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 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 (see Section 9.3.1.1). AEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs within 1 month after each vaccination will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs as described in Section 9.3.1.1. There is no Tier 1 event identified for BNT162b2 at this stage. For Tier 2 AEs, the between-group difference and 95% CIs will be calculated for 1 month after vaccination with SIIV and BNT162b2 at Visit 1 for the coadministration group vs 1 month after vaccination with SIIV and saline at Visit 1 for the separate-administration group, and for 1 month after vaccination with SIIV and BNT162b2 at Visit 1 for the coadministration group vs 1 month after vaccination with BNT162b2 at Visit 2 for the separate-administration group. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the first vaccination to 1 month after the last vaccination will be provided for each vaccine group.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
BNT162b2 immunogenicity	**GMCs/GMTs of full-length S-binding IgG levels and SARS-CoV-2–neutralizing titers** GMCs/GMTs and associated 2-sided 95% CIs at before vaccination and 1 month after vaccination with BNT162b2 will be provided for each vaccine group using the statistical methods described in Section 9.3.1.2.3. **GMFR of full-length S-binding IgG levels and SARS-CoV-2–neutralizing titers from before vaccination to 1 month after vaccination with BNT162b2**

Endpoint	Statistical Analysis Methods
	GMFR and the associated 2-sided 95% CIs will be provided for each vaccine group using the statistical methods described in Section 9.3.1.2.2.
SIIV immunogenicity	**GMTs of the strain-specific HAI titers and H3N2-neutralizing antibody titers** For each influenza strain, GMTs and the associated 2-sided 95% CIs at before vaccination and 1 month after vaccination with SIIV will be calculated for each vaccine group. **GMFR of the strain-specific HAI titers and H3N2-neutralizing antibody titers from before vaccination to 1 month after vaccination with SIIV** For each influenza strain, GMFR and the associated 2-sided 95% CIs will be calculated for each vaccine group.

9.3.4. Tertiary/Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
SIIV immunogenicity	**Percentage of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV** For each influenza strain, counts, percentages, and the associated Clopper-Pearson 95% CIs of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV will be provided for each vaccine group. **Percentage of participants with strain-specific HAI seroconversion 1 month after vaccination with SIIV** Seroconversion is defined as: • an HAI titer <1:10 before SIIV vaccination and an HAI titer ≥1:40 1 month after SIIV vaccination or • an HAI titer ≥1:10 before vaccination and a minimum 4-fold rise in HAI titer 1 month after SIIV vaccination. For each influenza strain, counts and percentages of participants with strain-specific HAI titer seroconversion 1 month after vaccination with SIIV will be provided for each vaccine group. The associated Clopper-Pearson 95% CIs will also be provided.

Endpoint	Statistical Analysis Methods
	Percentage of participants with H3N2 neutralization seroprotection 1 month after vaccination with SIIV **Percentage of participants with H3N2 neutralization seroconversion 1 month after vaccination with SIIV** The definitions of H3N2 neutralization seroprotection and seroconversion will be described in the SAP when H3N2 neutralization assay information becomes available. Counts and percentages of participants with H3N2 neutralization seroprotection and seroconversion 1 month after vaccination with SIIV will be provided for each vaccine group. The associated Clopper-Pearson 95% CIs will also be provided.

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.

9.5. Sample Size Determination

The sample size calculation is based on the primary efficacy estimands and corresponding endpoints: full-length S-binding IgG levels and strain-specific HAI titers. Table 5 presents the power to demonstrate noninferiority of the immune responses elicited by BNT162b2 and SIIV from the coadministration group to the separate-administration group. If the GMR of the coadministration group to the separate-administration group is 0.9 for SARS-CoV-2 full-length S-binding IgG and each influenza strain, with assumed standard deviations for each endpoint, a sample size of 450 evaluable participants per group will provide an overall power of 90.7% to declare noninferiority for all coprimary endpoints. Assuming a nonevaluable rate of 20%, the study will randomize approximately 1126 participants to achieve 450 evaluable participants in each group.

Table 5. Power Calculations for NI of the Coadministration Group to the Separate-Administration Group in SARS-CoV-2 Full-Length S-Binding IgG Levels and HAI Titers

Endpoint	NI Margin	SD in Natural Log Scale[a]	Power
			Assumed GMR=0.9 N=450 Evaluable/Group
SARS-CoV-2 full-length S-binding IgG	1.5-fold	1.05	98.8%
HAI titers			
A/H1N1	1.5-fold	1.05	98.8%
A/H3N2	1.5-fold	1.07	98.5%
B/Brisbane	1.5-fold	1.13	97.4%
B/Massachusetts	1.5-fold	1.16	96.8%
All[b]			**90.7%**

Abbreviations: GMR = geometric mean ratio; HAI = hemagglutination inhibition assay; IgG = immunoglobulin G; NI = noninferiority; S-binding = spike protein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Assay SDs for SARS-CoV-2 full-length S-binding IgG were based on the 1-month post–Dose 2 immunogenicity results from the C4591020 study (18-55 years of age), and the C4591001 study, Phase 2, in the 56-85-year age group; assay SDs for HAI endpoints were based on results on Afluria Quad.[32]

b. "All" = product of each power.

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

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

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

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date 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 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 who will review cumulative unblinded data throughout the study. 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.

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 Data Management 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 Emergency Contact Card (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

A pregnancy test will be performed at times defined in the SoA section of this protocol: Visit 1 (Vaccination 1/Day 1) and Visit 2 (Vaccination 2/28 to 42 days after Vaccination 1).

- 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 female participants of childbearing potential.

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 <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 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

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.

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 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 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

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 when having sexual intercourse with a woman of childbearing potential 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 using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:.

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
     - 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.

The following contraceptive methods are appropriate for this study:

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 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.

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

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 Schedule of Activities 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. Review and record contraceptive method if applicable. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 5.3.1.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.7. Appendix 7: 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.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (22 December 2021)

Overall Rationale for the Amendment: The BNT162b2 booster rollout in southern hemisphere countries will significantly reduce the pool of potential study participants ≥65 years of age because the majority will be due to receive their BNT162b2 booster prior to study start. The age eligibility of this study has been modified to include a younger age group who will be eligible for the booster vaccination during the planned study recruitment period. CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Study title, Section 1.1 (Synopsis), Section 2.1 (Study Rationale), Section 4.1 (Overall Design), Section 5.1 (Inclusion Criteria)	Updated age eligibility to include adults 18 through 64 years of age (stratified by age group [18-49 years and 50-64 years] and the removed ≥65-year age group.	Updated to mitigate risk to the achieving recruitment target.
Section 9 (Statistical Considerations)	Updated sample size calculations with new assumptions on assay SDs in Table 5. An additional reference (19) was added for assay SDs of HAI endpoints based on Afluria Quad.	Modified to reflect younger age group and comparator SIIV.
	Added a linear regression model to calculate GMR for the primary immunogenicity endpoints.	Updated to accommodate added stratifications (age and timing of the second dose of BNT162b2 prior to Visit 1) in the randomization of the study design.
	Revised the names of immunogenicity populations.	Updated to match the wording of the objectives.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 (Schema), Section 5.1 (Inclusion Criteria)	Updated eligibility criteria to include participants who have received their second dose of 30 µg BNT162b2 90 to 365 days before Visit 1 (Day 1).	Updated to accommodate potential shorter booster intervals because of emerging VOCs.
Section 1 (Protocol Summary), Section 3 (Objectives, Estimands, and Endpoints), Section 4.1 (Overall Design), Section 8 (Study Assessments and Procedures), Section 8.5.2 (Retained Research Samples for Genetics), Section 8.9.2 (Visit 2 – 1-Week Follow-Up Visit), Section 8.9.4 (Visit 4 – 1-Week Follow-Up Visit), Section 9 (Statistical Considerations), Section 10.5 (Appendix 5: Genetics)	CCI [redacted]	Removed for operational reasons.
Section 1.3 (SoA), Section 5.2 (Exclusion Criteria), Section 6.8.2 (Permitted During the Study), Section 8 (Study Assessments and Procedures), Section 10.2 (Clinical Laboratory Tests)	Added pregnancy test for WOCBP and updated eligibility criteria to exclude women who are pregnant or breastfeeding.	Updated requirements due to younger age group.

10.9. Appendix 9: 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
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
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
eSAE	electronic serious adverse event
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise

Abbreviation	Term
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition
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
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
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
IV	intravenous(ly)
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
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NI	noninferiority
NIMP	noninvestigational medicinal product
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
CCI	[redacted]
PI	principal investigator
PPE	personal protective equipment
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit

[redacted]

Abbreviation	Term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
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
SIIV	seasonal inactivated influenza vaccine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCR	T-cell receptor
Th1	T-helper type 1
TOC	table of contents
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

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