A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEALTHY PREGNANT WOMEN 18 YEARS OF AGE AND OLDER

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-005444-35
Protocol Number:	C4591015
Phase:	Phase 2/3

Short Title: A Phase 2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 2	02 March 2021	• Section 1.3.1 and Section 1.3.2: expanded the 1-month postdelivery visit window by 1 week to allow for potential earlier vaccination of BNT162b2 to participants originally randomized to receive placebo. • Section 1.3.3: removed "equivalent visit number for maternal participants" from the Infant SoA since this will differ for maternal participants originally randomized to placebo who will go on to receive BNT162b2 at 1 month after delivery and follow a different SoA. • Section 2.3: added a sentence to clarify that the protocol is a PASS. • Section 5.1.1: corrected the calculation of GA in the third trimester, replacing "second trimester" with "third trimester," and updated the discrepancy of days between the LMP-determined GA from >10 to >21 days. • Removed references to thumbprinting the ICD, since illiterate participants will not be enrolled from certain regions. • Clarified in Section 8.2.2 that field workers would be used in the case of poor network connection for e-diary completion. • Section 5.1.1, Section 8.16.3, and Section 10.4: added criteria for inclusion of maternal participants with stable HIV, hepatitis B, or hepatitis C in Phase 3.

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

		• Updated the Objectives, Estimands, and Endpoints to add a safety objective for the first 600 randomized maternal participants to support interim analysis/submission report.
		  ◦ Per CBER feedback, updated the term "NI" to "immunobridging" to describe the immunogenicity comparison between nonrandomized populations in the protocol.
		  ◦ Added a footnote to clarify that HIV-infected participants will not be included in analyses of the objectives. Analyses among HIV-infected women and their infants will be summarized separately.
		• Section 8.1.1 and Section 8.13.1: added a second definition of symptoms of severe COVID-19 disease per the CDC definition.
		• Section 8.2.3: clarified that stopping rules are in place during Phase 2 only, with no overlap into Phase 3.
		  ◦ Clarified that a study pause may not prevent administration of Dose 2 for enrolled participants.
		  ◦ Modified stopping rule 7 to include a trigger of preterm premature rupture of membranes.
		  ◦ Stopping rule 4: removed assessment of laboratory abnormalities, as these data are not collected in this study.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Section 8.11.1, Visit 1: removed the requirement of a repeat fetal scan to clarify that an earlier scan done at ≥18 weeks' GA can be used to confirm singleton pregnancy and rule out fetal anomalies. • Section 8.15: clarified that exclusion criterion 2 is not met if the participant meets the criteria for confirmed COVID-19 with or without symptoms and can receive Vaccination 2. • Section 8.16: to align with current recommendations, investigators may exercise judgment on review of inclusion and exclusion criteria ahead of vaccination with BNT162b2 for participants who originally received placebo. • Section 8.3.1 and Section 8.3.7: inserted language to clarify that potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. • Appendix 3: removed an erroneous partially completed sentence from the second paragraph.
Protocol amendment 1	28 January 2021	• Based on availability of BNT162b2 in high-risk pregnant women and evidence of safety in the real-world setting, the sentinel cohort of N=50 in Phase 2 was removed. • Based on feedback from an external advisory board, inclusion criterion 10 was updated to allow enrollment of participants with a prepregnancy BMI of ≤40 kg/m^2.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Clarified language in inclusion criterion 1 that GA dating for maternal participants who underwent assisted reproduction technology can be referenced in the SRM. • Corrected the list of prohibited medications under Section 6.5.1. • Clarified language in the Objectives, Estimands, and Endpoints table for consistency. • Added exploratory objectives to evaluate incidence rates of COVID-19 and asymptomatic SARS-CoV-2 infection through the entire follow-up among the maternal participants receiving BNT162b2. • Updated the VE assessment to reflect the reduced accrual of time following the unblinding of participants at 1 month after delivery. • Clarified the unblinding at 1 month after delivery for participants originally randomized to placebo who go on to receive BNT162b2. • Updated Section 2.3, Benefit-Risk Assessment, to include data from the DART studies. • In line with current recommendations, removed the requirement to discontinue study intervention because of a diagnosis of COVID-19 during the study. • Added the requirement to record antipyretic medication in the e-diary during the 7-day vaccination period, as this was omitted in error.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added editorial changes in the document to clarify where field workers/site staff may be required to call/visit maternal participants at home (applicable to regions where illiterate participants may be enrolled). • Clarified that participants originally randomized to placebo who go on to receive BNT162b2 at 1 month after delivery will not participate in surveillance for asymptomatic SARS-CoV-2 infection. • Clarified that AEs will be collected from the signing of the ICD to 1 month after Vaccination 4 (Visit 103) for those maternal participants who originally received placebo and who go on to receive BNT162b2 at 1 month after delivery.
Original protocol	21 December 2020	N/A

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older

Rationale

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the WHO and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to SARS virus isolates than to another coronavirus infecting humans, the MERS virus. SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic. Global case rates and deaths have continued to increase, with the United States reporting the most cases and deaths of any other country. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to prevent SARS-CoV-2 infections or the disease it causes, COVID-19.

Pregnant women are at risk for acquiring SARS-CoV-2 infection and COVID-19. Pregnancy may confer increased risk of severe COVID-19 because of physiological changes during pregnancy that can increase susceptibility to respiratory infections and subsequent rapid progression to respiratory failure. Additionally, pregnant women with COVID-19 have been reported to have higher rates of preterm birth, cesarean delivery, fetal distress, and infants requiring neonatal intensive care. Prevention of SARS-CoV-2 infection and COVID-19 is critically important in pregnant women.

Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BNT162b2 is a SARS-CoV-2–RNA-LNP vaccine based on a platform of modRNA with blunted innate immune sensor–activating capacity and augmented expression encoding the P2 S.

This study will describe the safety of BNT162b2 in pregnant women and their infants. It will also assess the immunogenicity of BNT162b2 in pregnant women, the transfer of antibody to their infants, and the kinetics of antibody transfer in the infant.

Objectives, Estimands, and Endpoints

Objectives[a]	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety and tolerability of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation in the first approximately 600 randomized maternal participants.	In maternal participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of maternal participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 through 1 month after Dose 2 • SAEs from Dose 1 through 1 month after delivery	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation.	In maternal participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of maternal participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 through 1 month after Dose 2 • SAEs from Dose 1 through 1 month after delivery	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
To demonstrate the immunobridging of the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation to the immune response in nonpregnant women 18 years of age or older from the C4591001 study without evidence of past SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable maternal participants) and no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection: • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in pregnant women to those in nonpregnant women 1 month after Dose 2	• SARS-CoV-2 neutralizing titers
To demonstrate the immunobridging of the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks'	In maternal participants complying with the key protocol criteria (evaluable participants): • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in pregnant women to	• SARS-CoV-2 neutralizing titers

Objectives[a]	Estimands	Endpoints
gestation to the immune response in nonpregnant women 18 years of age or older from the C4591001 study with and without evidence of prior SARS-CoV-2 infection.	those in nonpregnant female participants 1 month after Dose 2	
Secondary	**Secondary**	**Secondary**
If at least 12 cases are observed: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation without evidence of prior SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection: • 100 × (1 – IRR) [ratio of active vaccine to placebo]	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
If at least 12 cases are observed: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation with and without evidence of prior SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable participants): • 100 × (1 – IRR) [ratio of active vaccine to placebo]	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation without evidence of prior SARS-CoV-2 infection.	In evaluable maternal participants without serological or virological evidence of prior SARS-CoV-2 infection: • 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion

Objectives[a]	Estimands	Endpoints
To describe the immune response over time and persistence of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation.	In maternal participants complying with the key protocol criteria (evaluable maternal participants) from each vaccine group: • GMCs/GMTs, at baseline (before Dose 1), 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery • GMFRs from baseline through 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers
To assess the safety of maternal immunization in infants born to maternal participants 18 years of age or older who were vaccinated with BNT162b2 during pregnancy.	In infants born to maternal participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of infants with: • Specific birth outcomes • AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age	• Specific birth outcomes • AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age
To describe the immune response in infants born to maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to evaluable maternal participants from each vaccine group: • GMCs and GMFRs, at birth and 6 months after delivery	• Full-length S-binding IgG levels
Exploratory	**Exploratory**	**Exploratory**
To describe the incidence of confirmed COVID-19 among maternal participants who were vaccinated with BNT162b2.	In maternal participants who received BNT162b2 (at initial randomization and at 1 month after delivery): • Incidence per 1000 person-years of follow-up	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of asymptomatic SARS-CoV-2 infection through 6 months after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation with BNT162b2 at initial randomization and without	In maternal participants who received BNT162b2 at initial randomization and without evidence of prior SARS-CoV-2 infection: • Incidence per 1000 person-years of follow-up	• Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion

Objectives[a]	Estimands	Endpoints
evidence of prior SARS-CoV-2 infection.		
To describe the serological responses among maternal participants to the BNT162b2 vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19	In each subset of evaluable maternal participants from each vaccine group with: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection but no confirmed COVID-19 • GMCs/GMTs and GMFRs at baseline, 1 month after Dose 2, at delivery, and 6 months after delivery	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the immune response to prophylactic BNT162b2 between Dose 1 and Dose 2 when administered to maternal participants 18 years of age or older vaccinated at 27 to 34 weeks' gestation in the Phase 2 portion of the study.	In evaluable maternal participants: • GMCs/GMTs at baseline and before Dose 2 • GMFRs from baseline to before Dose 2	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group, based on the breastfeeding status: • GMCs and GMFRs, at birth and 6 months after delivery	• Full-length S-binding IgG levels
To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to maternal participants receiving at least 1 dose of study intervention from each vaccine group, based on the breastfeeding status, the percentage of infants with: • AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age	• AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age
To describe the incidence of confirmed COVID-19 in infants born to maternal participants who were vaccinated with BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group: • Incidence rate of infant participants with confirmed COVID-19	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Objectives[a]	Estimands	Endpoints
To describe MIS-C cases in infants born to maternal participants who were vaccinated with BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group: • Incidence rate of MIS-C	• MIS-C incidence per 1000 person-years of follow-up

a. HIV-infected participants will not be included in analyses of the objectives, but in separate exploratory analyses. Analyses among HIV-infected women and their infants will be summarized separately.

Overall Design

This will be a global Phase 2/3, randomized, placebo-controlled, observer-blind study evaluating the safety, tolerability, and immunogenicity of 30 µg of BNT162b2 or placebo administered in 2 doses, 21 days apart, in approximately 4000 healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks' gestation. Participants will be randomized 1:1 to receive BNT162b2 or placebo (saline).

The Phase 2 portion of the study will include approximately 350 pregnant women randomized 1:1 to receive BNT162b2 or placebo (saline) at 27 to 34 weeks' gestation. The IRC will review safety data through 7 days after the second dose for all Phase 2 participants and if BNT162b2 is deemed safe and tolerable, enrollment in Phase 3 will commence.

The Phase 3 portion of this study will assess the safety, tolerability, and immunogenicity of BNT162b2 among pregnant women enrolled at 24 to 34 weeks' gestation.

Maternal participants who originally received placebo will receive BNT162b2 at defined time points as part of the study.

Number of Participants

Approximately 350 healthy pregnant women will be enrolled in the Phase 2 portion of the study. Approximately 3650 healthy pregnant women will be enrolled in the Phase 3 portion.

Intervention Groups and Duration

This study will evaluate a 2-dose (separated by 21 days) schedule of 30 µg of the investigational BNT162b2 RNA vaccine candidate (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S) for active immunization against COVID-19.

Healthy pregnant women will be randomized in a 1:1 ratio to receive a 2-dose schedule of either:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S) at a dose of 30 µg OR
- Normal saline solution for injection (0.9% NaCl injection).

Each maternal participant will participate in the study for approximately up to 10 months depending on the vaccine group to which she was randomized. Her infant will participate in the study for approximately 6 months. The study duration will be approximately 14 months.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will be used during the Phase 2 portion of the study to closely monitor safety.

The study will include stopping rules, which may result in a pause to study vaccination followed by a review and recommendation by the IRC.

The study will use an external DMC to monitor vaccine safety throughout the study.

Statistical Methods

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs, and SAEs, for each vaccine group. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. A 3-tier approach will be used to summarize AEs. The AEs, including SAEs, reported in the open-label follow-up period will be summarized separately from those reported during the blinded follow-up period for maternal participants. The safety objective related to infants born to maternal participants, including birth outcomes, AEs, SAEs, and AESIs, will be evaluated in a similar way.

There are 2 primary immunogenicity objectives; each will be evaluated by a formal hypothesis test for immunobridging of SARS-CoV-2 neutralizing titers 1 month after Dose 2 in a subset of maternal participants compared to a group of randomly selected nonpregnant women within the same age group from the C4591001 study. Both model-based and unadjusted GMRs will be provided along with associated 2-sided 95% CIs. The fixed sequential testing procedure will be used for type I error control. The comparison for participants without evidence of prior SARS-CoV-2 infection will be conducted first, and immunobridging success will be declared if the lower bound of the 2-sided 95% CI for the GMR of the pregnant women relative to the nonpregnant women is greater than 0.67. The immunobridging for participants with and without evidence of prior SARS-CoV-2 infection will be assessed only if the immunobridging success for participants without evidence of prior SARS-CoV-2 infection is declared.

Other immunogenicity objectives will be evaluated descriptively by GMTs/GMCs and GMFRs of full-length S-binding IgG levels and/or SARS-CoV-2 neutralizing titers and associated 2-sided 95% CIs.

The secondary efficacy objectives are to evaluate VE against the confirmed COVID-19 illness during the blinded follow-up period, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. Hypothesis testing will be conducted only if at least 12 cases are accrued.

VE against asymptomatic infection will be evaluated descriptively.

The incidence rates of confirmed COVID-19 and asymptomatic infection per 1000 person-years of follow-up in maternal participants after their receipt of BNT162b2 throughout the study will be provided with the associated 2-sided 95% CIs.

The incidence rate of confirmed COVID-19 and incidence rate of confirmed MIS-C in infant participants, and associated 2-sided 95% CIs, will also be provided according to the vaccine group to which the maternal participants were randomized.

1.2. Schema

Not applicable.

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.

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 8 (6-month postdelivery visit, the final study visit) or Visit 103 (1-month follow-up phone contact) that potential COVID-19 symptoms are reported, including MIS-C.

1.3.1. Schedule of Activities for Maternal Participants

Visit Number (Maternal Participants)	1	2	3	4	5	6	7	8	Unplanned	Unplanned
Visit Description	Screening: -28 Days to Vaccination 1	Vaccination 2	2-Week Post–Vaccination 2 Follow-up[a]	1-Month Post–Vaccination 2 Follow-up[a]	Delivery	1-Week Postdelivery Follow-up Call	1-Month Postdelivery Follow-up[b]	6-Month Postdelivery Follow-up For Participants Originally Randomized to Receive BNT162b2	Potential COVID-19 Illness Visit[c]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1 Visit 1	19 to 23 Days After Visit 1	11 to 17 Days After Visit 2	28 to 35 Days After Visit 2	Varies	7 to 10 Days After Delivery	21 to 35 Days After Delivery	160 to 200 Days After Delivery	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**		
Obtain informed consent	X									
Assign single participant identifier	X									

Visit Number (Maternal Participants)	1	2	3	4	5	6	7	8	Unplanned	Unplanned
Visit Description	Screening: -28 Days to Vaccination 1	Vaccination 2	2-Week Post–Vaccination 2 Follow-up[a]	1-Month Post–Vaccination 2 Follow-up[a]	Delivery	1-Week Postdelivery Follow-up Call	1-Month Postdelivery Follow-up[b]	6-Month Postdelivery Follow-up For Participants Originally Randomized to Receive BNT162b2	Potential COVID-19 Illness Visit[c]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1 Visit 1	19 to 23 Days After Visit 1	11 to 17 Days After Visit 2	28 to 35 Days After Visit 2	Varies	7 to 10 Days After Delivery	21 to 35 Days After Delivery	160 to 200 Days After Delivery	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**		
Obtain demography	X									
Record current alcohol and tobacco usage	X									
Obtain medical history, including obstetric and gestational history	X									
Phase 3 only: For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X		X	X		
Record LMP and EDD	X									
Measure vital signs	X	X		X						
Perform physical examination	X									
Perform targeted physical examination		X		X						
Perform obstetric examination	X	X		X						
Perform obstetric ultrasound	X									
Record nonstudy vaccine information	X	X	X	X	X	X	X	X		
Record concomitant medication associated with an adverse event or serious adverse event	X	X	X	X	X	X	X	X[d]		

Visit Number (Maternal Participants)	1	2	3	4	5	6	7	8	Unplanned	Unplanned
Visit Description	**Screening: -28 Days to Vaccination 1**	**Vaccination 2**	**2-Week Post–Vaccination 2 Follow-up[a]**	**1-Month Post–Vaccination 2 Follow-up[a]**	**Delivery**	**1-Week Postdelivery Follow-up Call**	**1-Month Postdelivery Follow-up[b]**	**6-Month Postdelivery Follow-up For Participants Originally Randomized to Receive BNT162b2**	**Potential COVID-19 Illness Visit[c]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1 Visit 1**	**19 to 23 Days After Visit 1**	**11 to 17 Days After Visit 2**	**28 to 35 Days After Visit 2**	**Varies**	**7 to 10 Days After Delivery**	**21 to 35 Days After Delivery**	**160 to 200 Days After Delivery**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**		
Record prohibited medications									X	X
Review eligibility criteria	X	X								
Review temporary delay criteria	X	X								
Review continued eligibility			X	X	X	X	X	X		
Explain/review participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X									
Record systemic events at baseline in the e-diary	X									
Assign participant randomization and container number	X									
Collect blood sample for immunogenicity assessment (~20 mL per blood sample)	X	X[e]	X	X	X			X		X
Obtain nasal (midturbinate swab)	X	X							X[d]	
Administer study intervention	X	X								

Visit Number (Maternal Participants)	1	2	3	4	5	6	7	8	Unplanned	Unplanned
Visit Description	**Screening: -28 Days to Vaccination 1**	**Vaccination 2**	**2-Week Post–Vaccination 2 Follow-up[a]**	**1-Month Post–Vaccination 2 Follow-up[a]**	**Delivery**	**1-Week Postdelivery Follow-up Call**	**1-Month Postdelivery Follow-up[b]**	**6-Month Postdelivery Follow-up For Participants Originally Randomized to Receive BNT162b2**	**Potential COVID-19 Illness Visit[c]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1 Visit 1**	**19 to 23 Days After Visit 1**	**11 to 17 Days After Visit 2**	**28 to 35 Days After Visit 2**	**Varies**	**7 to 10 Days After Delivery**	**21 to 35 Days After Delivery**	**160 to 200 Days After Delivery**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X								
Provide/ensure participant has a thermometer and measuring device	X	X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period of 7 days following study intervention administration)	◄——►	◄——►								
Review ongoing reactogenicity e-diary symptoms with participant and obtain stop dates		X	X							
Record pregnancy outcome information					X	X				
Record AEs and SAEs as appropriate[f]	X	X	X	X	X[d]	X[d]	X	X[d]	X[d]	X[d]
Collect e-diary or assist the participant to delete application								X		

Visit Number (Maternal Participants)	1	2	3	4	5	6	7	8	Unplanned	Unplanned
Visit Description	Screening: -28 Days to Vaccination 1	Vaccination 2	2-Week Post–Vaccination 2 Follow-up[a]	1-Month Post–Vaccination 2 Follow-up[a]	Delivery	1-Week Postdelivery Follow-up Call	1-Month Postdelivery Follow-up[b]	6-Month Postdelivery Follow-up For Participants Originally Randomized to Receive BNT162b2	Potential COVID-19 Illness Visit[c]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1 Visit 1	19 to 23 Days After Visit 1	11 to 17 Days After Visit 2	28 to 35 Days After Visit 2	Varies	7 to 10 Days After Delivery	21 to 35 Days After Delivery	160 to 200 Days After Delivery	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Type of Visit	Clinic	Clinic	Clinic	Clinic	Hospital	Phone Call	Clinic	Clinic		
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)									X	X

Abbreviations: EDD = estimated delivery date; HIV = human immunodeficiency virus; LMP = last menstrual period.

a. The 2-week postvaccination follow-up and 1-month postvaccination follow-up visits will not be performed if delivery occurs before the visits. If delivery occurs before Vaccination 2, the second dose should be given as soon as possible after delivery. Once delivery occurs, the visit windows are calculated based on the delivery date.
b. All maternal participants will be unblinded. Placebo recipients will be given BNT162b2 and move to follow the procedures in Section 1.3.2.
c. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
d. Only AEs occurring up to 48 hours after each blood draw and nasal midturbinate swab collection must be recorded.
e. Prevaccination blood samples for immunogenicity will be drawn from maternal participants in Phase 2 only.
f. The investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through 1 month after Vaccination 2. From 1 month after Vaccination 2 until the 6-month postdelivery follow-up, SAEs will be collected.

1.3.2. Schedule of Activities for Maternal Participants Who Were Originally Assigned to Placebo

Visit Number (Maternal Participants)	101	102	103
Visit Description	**1-Month Postdelivery Follow-up Vaccination 3**	**Vaccination 4**	**1-Month Telephone Contact Follow-up**
Visit Window (Days)	**21 to 35 Days After Delivery**	**19 to 23 Days After Visit 101**	**28 to 35 Days After Visit 102**
Type of Visit	**Clinic**	**Clinic**	**Phone Call**
Confirm the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required	X		
Collect prohibited medication use	X	X	X
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X
Review and consider eligibility	X	X	
Review temporary delay criteria	X	X	
Collect blood sample for immunogenicity assessment	~20 mL		
Obtain nasal (midturbinate) swab	X	X	
Obtain vaccine vial allocation via IRT	X	X	
Administer BNT162b2	X	X	
Assess acute reactions for at least 30 minutes after study intervention administration	X	X	
Collect AEs and SAEs as appropriate	X	X	X
Contact the participant by telephone			X

1.3.3. Schedule of Activities for Infant Participants

Visit Number (Infant Participants)	1	2	3		
				Unplanned	Unplanned
Visit Description	Delivery	1-Week Postdelivery Follow-up	6-Months-of-Age Follow-up	Potential COVID-19 Illness Visit	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Varies	7 to 10 Days After Delivery	160 to 200 Days After Delivery	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Type of Visit	Hospital	Phone Call	Clinic		
Assign single participant identifier	X				
Record demography and available birth information	X				
Measure vital signs	X				
Perform physical examination	X				
Record concomitant medication associated with an adverse event/serious adverse event	X	X	X		
Review eligibility	X				
Review continued eligibility		X	X		
Record breastfeeding information		X	X		
Collect blood sample for immunogenicity assessment (up to ~5 mL per blood sample depending on weight)			X		X
Cord blood sample (~10 mL) for immunogenicity assessment	X[a]				
Record adverse events	X	X[b]	X[b]	X	X
Record serious adverse events and adverse events of special interest	X	X	X	X	X
Collect prohibited medication use				X	X
Obtain nasal swab				X	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)				X	X

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

a. If cord blood is unavailable, a blood sample may be collected from the infant participant up to 72 hours after birth but preferably within 24 hours after birth.
b. Active AE collection through 1 month of age.

2. INTRODUCTION

The BNT162b2 RNA-based COVID-19 vaccine is currently being investigated for prevention of COVID-19 in healthy pregnant women.

2.1. Study Rationale

The purpose of the study is to describe the safety, tolerability, and immunogenicity of BNT162b2 RNA-based COVID-19 vaccine against COVID-19 in healthy pregnant women. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Pregnant women are at risk of acquiring SARS-CoV-2 infection, developing COVID-19 and COVID-19–associated complications. Given the global crisis of COVID-19 and fast expansion of the disease globally, the rapid development of an effective vaccine for use in this population is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the WHO and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to SARS virus isolates than to another coronavirus infecting humans, the MERS virus.[1,2]

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries, and on 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[3] On 16 December 2020, The Center for Systems Science and Engineering at Johns Hopkins University reported more than 73 million cases globally, with over 1.6 million deaths from 191 countries. Global case rates and deaths have continued to increase, with the United States reporting the most cases and deaths of any other country. There are currently no vaccines broadly available to prevent SARS-CoV-2 infections or the disease it causes, COVID-19.[4]

Pregnant women are at risk for acquiring SARS-CoV-2 infection and COVID-19.[5,6,7] Pregnancy may confer increased risk of severe COVID-19 because of physiological changes during pregnancy that can increase susceptibility to respiratory infections and subsequent rapid progression to respiratory failure.[8] Additionally, pregnant women with COVID-19 have been reported to have higher rates of preterm birth, cesarean delivery, fetal distress, and infants requiring neonatal intensive care.[8,9,10,11] While COVID-19 in children is reported less commonly than in adults, infants <1 year of age, if infected with SARS-CoV-2, may be at increased risk of severe disease, and younger age groups have increasing rates of COVID-19–associated hospitalization.[12,13] Prevention of SARS-CoV-2 infection and COVID-19 is critically important in pregnant women, and maternal immunization may confer some protection to their infants.

Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[14,15] The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.[14,15]

There are no ongoing COVID-19 vaccine studies including pregnant women. Vaccination of pregnant women has been used globally to protect both women and their infants against influenza and as a mechanism to protect infants against pertussis. Several studies have demonstrated that maternal immunization is safe for both mother and infant and an important strategy to protect pregnant women and their infants against infectious diseases. Currently maternal immunization studies are being conducted as part of the development of novel RSV and GBS vaccines.[16,17]

BNT162b2 is a SARS-CoV-2–RNA-LNP vaccine based on a platform of modRNA with blunted innate immune sensor–activating capacity and augmented expression encoding the P2 S.

This study will describe the safety of BNT162b2 in pregnant women and their infants. It will also assess the immunogenicity of BNT162b2 in pregnant women, the transfer of antibody to their infants, and the kinetics of antibody transfer in the infant.

2.2.1. Clinical Overview

Prior to this study, clinical data from BNT162b2 established a favorable safety profile characterized by mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to >19,000 people[18] at the 30-µg dose level using a 2-dose schedule since the C4591001 Phase 1/2/3 study started in the United States and other countries. BNT162b2 was also evaluated in the BNT162-01 study conducted in Germany by BioNTech, at dose levels between 1 µg and 100 µg.[19]

Study C4591001 is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals. The study consists of 2 parts: Phase 1: to identify 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 study for the selected vaccine candidate (BNT162b2).

The Phase 1 study population included healthy participants 18 to 55 years and 65 to 85 years of age. Enrollment in C4591001 Phase 1 is complete and, although follow-up continues, the available safety data from Phase 1 participants in Study C4591001 show that BNT162b2 reactogenicity, AEs, and laboratory results were consistent with those commonly associated with vaccination. The observed reactogenicity was generally mild or moderate (primarily pain at the injection site) and short-lived. The local reactions tended to be more frequent after the second dose. There was no redness or swelling reported by participants in the 65- to 85-year age group who received BNT162b2.[20]

Regarding systemic events, 17% of the 18- to 55-year-old participants and 8% of those in the 65- to 85-year age group reported fever (≥38.0°C to 38.9°C) after the second dose of 30 µg of BNT162b2. Severe systemic events (fatigue, headache, chills, muscle pain, and joint pain) were reported in small numbers of younger recipients of this vaccine candidate, but no severe systemic events were reported in older recipients, and no Grade 4 systemic events were reported.[20]

No unexpected AEs or SAEs were reported. Through 1 month after receipt of the second vaccine, AEs that were considered by investigators to be related to the study intervention were reported in 25% of participants 18 to 55 years of age who received 30 µg of BNT162b2; no AEs were reported by the older population who received the same dose.[20]

The available immunogenicity data from Phase 1 participants show that BNT162b2 induced a robust IgG-binding response to S1 and SARS-CoV-2 neutralizing response. Immunogenicity also substantially increased following the second dose of vaccine. BNT162b2 induces a strong antigen-specific T_H1-skewed CD4+ response and a strong antigen-specific CD8+ response.

Based on the safety, tolerability, and immunogenicity data generated from Phase 1, the vaccine candidate selected for the Phase 2/3 part of the study was BNT162b2 at a dose of 30 µg. This phase of the study is currently ongoing and is evaluating the efficacy of the study intervention.

The Phase 2/3 portion of C4591001 is ongoing in participants ≥12 years of age.

There are 2 primary efficacy endpoints in the Phase 2/3 part of the C4591001 study. The first is to evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection, and the second is to evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants regardless of evidence of prior SARS-CoV-2 infection. Cases of COVID-19 are defined by the presence of specified symptoms plus a NAAT for SARS-CoV-2 at least 7 days following the second dose of vaccine.

The primary safety objective includes definition of the safety profile of prophylactic BNT162b2 as measured by solicited local reactions and systemic events within 7 days after vaccination, AEs, and SAEs.

The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventive vaccines broadly available for pregnant women. While there were no data available from clinical trials on the use of BNT162 vaccines in pregnant women, preliminary data are available from the ongoing Phase 1/2/3 clinical trial evaluating the use of BNT162b2 30-µg doses administered 21 days apart in nonpregnant adults.

The Phase 2/3 portion of the C4591001 study has reached the final efficacy analysis and demonstrates that BNT162b2 is effective, with 95% observed VE, against COVID-19 among individuals 16 years of age and older. Safety evaluation is ongoing; however, ~19,000 participants have safety data available for at least 2 months of follow-up after the second dose. In general, BNT162b2 had a favorable safety profile. BNT162b2 recipients reported more reactogenicity events compared to placebo recipients. In general, local reactions were mostly mild to moderate in severity and resolved within 1 to 2 days after onset. Severe fatigue was reported in 3.8% of BNT162b2 recipients; however, these events were transient. Few participants in either group had severe AEs, SAEs, or AEs leading to withdrawal from the study.[18]

These data suggest a favorable risk/benefit profile in pregnant women. Anticipated AEs after vaccination in maternal participants are expected to be manageable using routine symptom-driven standard of care as determined by the investigators. As a result, the profile of these vaccine candidates supported initiation of this PASS clinical study. This interventional study is designated as a PASS, identified as Category 3 in the EU RMP, and is conducted as a conditional marketing approval commitment to the EMA and Swissmedic and an emergency use authorization commitment to the US FDA and numerous other health authorities under respective national emergency use legislation.

DART studies have been completed. In summary, administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose was associated with nonadverse effects (body weight, food consumption, and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the female rats or on embryo-fetal or postnatal survival, growth, or development in the offspring. An immune response was confirmed in female rats following administration of each vaccine candidate and these responses were also detectable in the offspring (fetuses and pups). Additional details are included in the IB.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[21]	• Phase 1 data from the C4591001 study demonstrated that the 30-µg dose had a tolerable reactogenicity profile.[18] • This study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. • All participants will be observed for at least 30 minutes after vaccination. • In addition, the study will enroll a smaller subset of pregnant women in Phase 2 (N=350) and have a review of 7-day safety data by an IRC before expansion of the study into Phase 3.
Unknown AEs with a novel vaccine.	There are limited data available because of the ongoing C4591001 study (Phase 1 completed, Phase 2/3 ongoing). To date, the safety and tolerability profile of BNT162b2 is consistent with what has been expected from nonclinical studies and clinical studies in other RNA-based compounds.[22,23]	• An IRC (in Phase 2) will review safety. Stopping rules will be in place for Phase 2, which may result in a pause to study vaccination followed by a review and recommendation by the IRC. • A DMC will be used throughout the study to review all safety data. • All participants will be observed for at least 30 minutes after vaccination. • AE and SAE reports will be collected from the signing of the ICD through 1 month after the second dose of vaccine. • In maternal participants who receive BNT162b2 1 month after delivery, AEs will be collected from the signing of the ICD to 1 month after Vaccination 4 (Visit 103) for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		those maternal participants who originally received placebo and go on to receive BNT162b2.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with RSV, feline coronavirus, and Dengue virus vaccines.	• Eligibility criteria will exclude any pregnant participants who have had a previous clinical (signs/symptoms only) or microbiological (signs/symptoms and positive SARS-CoV-2 NAAT result) diagnosis of COVID-19. • Monitoring for cases of COVID-19 developing during the study will be reported.
Potential for adverse obstetric and/or neonatal outcomes following vaccination.	There are no ongoing COVID-19 vaccine studies including pregnant women and, therefore, the potential for adverse obstetric and/or neonatal outcomes following vaccination while pregnant is unknown.	• Stopping rules for obstetric and neonatal AEs occurring after study vaccination and/or possibly deemed related to study vaccination in the Phase 2 portion of the trial. If a stopping rule is triggered, a pause of study vaccination will be put in place until there is a review of all relevant safety events and evaluation by the IRC.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	• Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. • Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the maternal participant performing a self-swab or obtaining a swab from her infant.
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 maternal participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic.
- Access to COVID-19 diagnostic and antibody testing.
- Contributing to research to help others in a time of global pandemic.
- Potential antibody protection for infants born to mothers who were vaccinated with COVID-19 vaccine.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives[a]	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety and tolerability of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation in the first approximately 600 randomized maternal participants.	In maternal participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of maternal participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 through 1 month after Dose 2 • SAEs from Dose 1 through 1 month after delivery	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation.	In maternal participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of maternal participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 through 1 month after Dose 2 • SAEs from Dose 1 through 1 month after delivery	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Objectives[a]	Estimands	Endpoints
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
To demonstrate the immunobridging of the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation to the immune response in nonpregnant women 18 years of age or older from the C4591001 study without evidence of past SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable maternal participants) and no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection: • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in pregnant women to those in nonpregnant women 1 month after Dose 2	• SARS-CoV-2 neutralizing titers
To demonstrate the immunobridging of the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation to the immune response in nonpregnant women 18 years of age or older from the C4591001 study with and without evidence of prior SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable participants): • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in pregnant women to those in nonpregnant female participants 1 month after Dose 2	• SARS-CoV-2 neutralizing titers
Secondary	**Secondary**	**Secondary**
If at least 12 cases are observed: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation without evidence of prior SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection: • 100 × (1 – IRR) [ratio of active vaccine to placebo]	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
If at least 12 cases are observed: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation with and without evidence of prior SARS-CoV-2 infection.	In maternal participants complying with the key protocol criteria (evaluable participants): • 100 × (1 – IRR) [ratio of active vaccine to placebo]	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT

Objectives[a]	Estimands	Endpoints
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation without evidence of prior SARS-CoV-2 infection.	In evaluable maternal participants without serological or virological evidence of prior SARS-CoV-2 infection: • 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion
To describe the immune response over time and persistence of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation.	In maternal participants complying with the key protocol criteria (evaluable maternal participants) from each vaccine group: • GMCs/GMTs, at baseline (before Dose 1), 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery • GMFRs from baseline through 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers
To assess the safety of maternal immunization in infants born to maternal participants 18 years of age or older who were vaccinated with BNT162b2 during pregnancy.	In infants born to maternal participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of infants with: • Specific birth outcomes • AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age	• Specific birth outcomes • AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age
To describe the immune response in infants born to maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to evaluable maternal participants from each vaccine group: • GMCs and GMFRs, at birth and 6 months after delivery	• Full-length S-binding IgG levels

Objectives[a]	Estimands	Endpoints
Exploratory	**Exploratory**	**Exploratory**
To describe the incidence of confirmed COVID-19 among maternal participants who were vaccinated with BNT162b2.	In maternal participants who received BNT162b2 (at initial randomization and at 1 month after delivery): • Incidence per 1000 person-years of follow-up	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of asymptomatic SARS-CoV-2 infection through 6 months after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation with BNT162b2 at initial randomization and without evidence of prior SARS-CoV-2 infection.	In maternal participants who received BNT162b2 at initial randomization and without evidence of prior SARS-CoV-2 infection: • Incidence per 1000 person-years of follow-up	• Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion
To describe the serological responses among maternal participants to the BNT162b2 vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19	In each subset of evaluable maternal participants from each vaccine group with: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection but no confirmed COVID-19 • GMCs/GMTs and GMFRs at baseline, 1 month after Dose 2, at delivery, and 6 months after delivery	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the immune response to prophylactic BNT162b2 between Dose 1 and Dose 2 when administered to maternal participants 18 years of age or older vaccinated at 27 to 34 weeks' gestation in the Phase 2 portion of the study.	In evaluable maternal participants: • GMCs/GMTs at baseline and before Dose 2 • GMFRs from baseline to before Dose 2	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers
To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group, based on the breastfeeding status: • GMCs and GMFRs, at birth and 6 months after delivery	• Full-length S-binding IgG levels

Objectives[a]	Estimands	Endpoints
To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to maternal participants receiving at least 1 dose of study intervention from each vaccine group, based on the breastfeeding status, the percentage of infants with: • AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age	• AEs from birth through 1 month of age • SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age
To describe the incidence of confirmed COVID-19 in infants born to maternal participants who were vaccinated with BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group: • Incidence rate of infant participants with confirmed COVID-19	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe MIS-C cases in infants born to maternal participants who were vaccinated with BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group: • Incidence rate of MIS-C	• MIS-C incidence per 1000 person-years of follow-up

a. HIV-infected participants will not be included in analyses of the objectives, but in separate exploratory analyses. Analyses among HIV-infected women and their infants will be summarized separately.

4. STUDY DESIGN

4.1. Overall Design

This will be a global Phase 2/3, randomized, placebo-controlled, observer-blind study in approximately 4000 healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks' gestation. This study will evaluate the safety, tolerability, and immunogenicity of 2 doses of BNT162b2 or placebo administered 21 days apart. The Phase 2 portion of the study will include approximately 350 pregnant women randomized 1:1 to receive BNT162b2 or placebo (saline) during their 27 to 34 weeks' gestation. Safety data through 7 days after the second dose (where Day 1 is the day of vaccination) for all Phase 2 participants will be reviewed by the Pfizer IRC and if BNT162b2 is deemed safe and tolerable, enrollment in the Phase 3 portion of the study will commence. The Phase 3 portion of this study will assess the safety, tolerability, and immunogenicity of BNT162b2 in 3650 pregnant women enrolled during their 24 to 34 weeks' gestation who will be randomized in a 1:1 ratio to receive BNT162b2 or placebo (saline). Maternal participants who originally received placebo will receive BNT162b2 at defined time points as part of the study.

The study is observer-blinded, as the physical appearance of the investigational vaccine and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded through the 1-month postdelivery visit for each maternal participant. At the study site, only the dispenser(s)/administrator(s) are unblinded.

Each maternal participant will participate in the study for approximately up to 10 months depending on the vaccine group to which she was randomized. Her infant will participate in the study for approximately 6 months. The study duration will be approximately 14 months.

For each placebo recipient who will go on to receive BNT162b2 and follow a new visit schedule (Section 1.3.2), she will participate in the study for up to 7 months, and her infant will participate in the study for approximately 6 months.

The study will use an external DMC throughout study conduct. A Pfizer IRC will be used during the Phase 2 portion of the study to closely monitor safety.

The study will include stopping rules, which may result in a pause to study vaccination followed by a review and recommendation by the IRC.

4.2. Scientific Rationale for Study Design

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Pregnant women are at risk of acquiring SARS-CoV-2 infection, developing COVID-19 and COVID-19–associated complications. Given the global crisis of COVID-19 and fast expansion of the disease globally, the rapid development of an effective vaccine for use in this population is of utmost importance.

This study is being conducted as a standard maternal immunization safety and immunogenicity clinical trial; however, additional surveillance for COVID-19 has been included as part of the study to assess efficacy (based on a minimal number of cases) as well as to monitor the potential risk of disease enhancement and severe disease in pregnant women and their infants with COVID-19. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

4.3. Justification for Dose

Based on data from the Phase 1 component of clinical trial C4591001, the BNT162b2 vaccine candidate was selected at a dose of 30 µg for Phase 2/3 evaluation in C4591001.

4.4. End of Study Definition

A participant and her infant are considered to have completed the study if they have completed all phases of the study, including the last visit.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. 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.

NOTE: In countries/locales where certain prenatal assessments are not routinely performed, prerandomization assessments and test results to confirm maternal participant eligibility for this clinical trial can be obtained and reviewed by the investigator or qualified designee up to 28 days prior to vaccination.

Maternal participants must provide informed consent prior to performing any procedures, including those that are being done exclusively to meet study eligibility criteria.

5.1.1. Maternal Participants

Age and Sex:

1. Healthy women ≥18 years of age who are between 24 0/7 and 34 0/7 weeks' gestation on the day of planned first vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications.

    a. **Phase 2** participants will include healthy women ≥18 years of age who are between **27 0/7 and 34 0/7** weeks' gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications.

GA will be documented based on one of the following composite criteria based on timing and availability of data on the LMP, ultrasound examination, and physical examination, for natural pregnancies. Please refer to the SRM for GA dating among women who underwent assisted reproduction technology. The earliest ultrasound data available during the current pregnancy should be used to establish GA:

a. **First-Trimester Data Available** (data obtained at ≤13 6/7 weeks):

- The date of the first day of the reported LMP may be used to establish the GA if corroborated by a first-trimester ultrasound.

- If there is a discrepancy of >7 days between the LMP-determined GA and a first-trimester ultrasound OR the LMP is uncertain/unknown, then the GA should be determined using the first-trimester ultrasound.

b. **Second-Trimester Data Available (data obtained at 14 0/7 to 27 6/7 weeks):**

- The date of the first day of the reported LMP may be used to establish the GA if corroborated by a second-trimester ultrasound or a physical examination including fundal height.

- If there is a discrepancy of >10 days between the LMP-determined GA and the second-trimester ultrasound OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound.

c. **Third-Trimester Data Available (data obtained at ≥28 weeks):**

- The date of the first day of the reported LMP may be used to establish the GA if corroborated by a third-trimester ultrasound or a physical examination including fundal height.

- If there is a discrepancy of >21 days between the LMP-determined GA and the third-trimester ultrasound OR if the LMP is uncertain/unknown, then the GA should be determined using the third-trimester ultrasound.

Type of Participant and Disease Characteristics:

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

3. Receiving prenatal standard of care based on country requirements.

4. Had an ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed, based on the investigator's judgment.

5. Healthy participants who are determined by medical history, physical examination, and clinical judgment to be appropriate for inclusion in the study. Note: Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.4.

6. Documented negative HIV antibody test (Phase 2 only), syphilis test, and HBV surface antigen test during this pregnancy and prior to randomization (Visit 1).

7. Intention to deliver at a hospital or birthing facility where study procedures can be conducted.

8. Expected to be available for the duration of the study and can be contacted by telephone during study participation.

9. Participant is willing to give informed consent for her infant to participate in the study.

Weight:

10. Prepregnancy BMI of ≤40 kg/m^2. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used.

Informed Consent:

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

5.1.2. Infant Participants

1. Evidence of a signed and dated ICD signed by the parent(s).

    - The maternal participant must sign an ICD for herself and her fetus/infant before taking part in the study. The father of the fetus/infant must sign an ICD if required by local requirements.

2. Parent(s) willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.2. Exclusion Criteria

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

5.2.1. Maternal Participants

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

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

4. Participants with known or suspected immunodeficiency.

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

6. **Phase 2 only: A prior or current** major illness of the mother or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response, including but not limited to the following:

    - Gestational hypertension or preeclampsia-eclampsia
    - Placental abnormality
    - Polyhydramnios or oligohydramnios
    - Significant bleeding or blood clotting disorder
    - Gestational diabetes
    - Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth
    - Prior stillbirth or neonatal death, prior low birth weight or preterm delivery, prior history of at least 3 miscarriages, prior pregnancies numbering greater than 5, or previous infant with a known genetic disorder or major congenital anomaly

7. **For Phase 2 only**: Maternal participants with a history of stable chronic diseases that are known to be associated with increased risk of obstetrical or neonatal complications (as defined above in exclusion criterion 6) should not be included.

8. **Phase 3: Current** major illness of the mother or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response, including but not limited to the following:

    - Uncontrolled gestational hypertension
    - Preeclampsia-eclampsia
    - Placental abnormality
    - Polyhydramnios or oligohydramnios
    - Significant bleeding or blood clotting disorder
    - Uncontrolled gestational diabetes

- Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth

- Prior stillbirth or neonatal death, preterm delivery (≤34 weeks), or previous infant with a known genetic disorder or major congenital anomaly.

Prior/Concomitant Therapy:

9. Previous vaccination with any coronavirus vaccine.

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

11. Receipt of blood/plasma products or immunoglobulin, from 60 days before administration of study intervention, or planned receipt through delivery, with 1 exception, anti-D immunoglobulin (eg, RhoGAM), which can be given at any time.

12. Current alcohol abuse or illicit drug use.

13. Participants who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the postvaccination blood draw.

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.

15. Previous participation in other studies involving study intervention containing LNPs.

Diagnostic Assessments:

16. Not applicable.

Other Exclusions:

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

18. Participants whose unborn baby has been fathered by investigational site staff members directly involved in the conduct of the study or their family members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study.

5.2.2. Infant Participants

1. Infant who is a direct descendant (eg, child or grandchild) of the study personnel.

5.3. Lifestyle Considerations

No restrictions required.

5.4. Screen Failures

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

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

5.5. Criteria for Temporarily Delaying Randomization/Study Intervention Administration

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

1. Current febrile illness (temperature 38.0°C [100.4°F]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;
    - New loss of taste/smell;
    - Sore throat;
    - Diarrhea;
    - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine in the previous 14 days.
3. Anticipated receipt of any seasonal or pandemic influenza vaccine in the 7 days after study intervention administration.

4. Receipt of a tetanus-, diphtheria-, and/or pertussis-containing vaccine in the previous 14 days.

5. Anticipated receipt of a tetanus-, diphtheria-, and/or pertussis-containing vaccine in the 7 days after study intervention administration.

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

6. STUDY INTERVENTION

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

The study will evaluate 2 doses of BNT162b2 or placebo administered 21 days apart for active immunization against COVID-19 in healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks' gestation. The Phase 2 portion of the study will include a subset (N= 350) of pregnant women during their 27 to 34 weeks' gestation.

The investigational RNA vaccine candidate or saline placebo are the 2 potential study interventions that may be administered to pregnant maternal participants (randomized 1:1):

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

- Normal saline (0.9% NaCl solution for injection)

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)	Saline Placebo
Type	Vaccine	Placebo
Dose Formulation	modRNA	Normal saline (0.9% NaCl solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	N/A
Dosage Level(s)	30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement.	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement.

6.1.1. Administration

Maternal participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 2) in accordance with the study's SoA (Section 1.3.1). Full details are described in the IP manual.

At 1 month after delivery, maternal participants who originally received placebo will receive 1 dose of BNT162b2 at each additional vaccination visit (Visits 101 and 102) in accordance with the SoA in Section 1.3.2.

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

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

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

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Maternal participants will be allocated (randomized) to a vaccine group as described below. The infants of the maternal participants will be assigned a participant number at birth.

Allocation of maternal 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 maternal participant number. The site personnel will then be provided with a vaccine assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the maternal participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

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

Maternal participants will be assigned to receive study intervention according to randomization scheme. Investigators will remain blinded to each maternal participant's assigned study intervention until 1 month after delivery.

6.3.2. Blinding of Site Personnel Until the 1-Month Postdelivery Visit

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 maternal participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate maternal participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidate and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the maternal study participants from identifying the study intervention type based on its appearance.

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

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.

To allow administration of BNT162b2 to maternal participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation at the 1-month postdelivery visit.

6.3.3. Blinding of Site Personnel Prior to the 1-Month Postdelivery Visit

To allow administration of BNT162b2 to maternal participants who originally received placebo, site staff will be unblinded to individual participants' original study intervention allocation at the 1-month postdelivery visit. Prior to unblinding maternal participants at the 1-month postdelivery visit, this is an 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 maternal participants, will be blinded to study intervention assignments until the 1-month postdelivery visit for each participant. In particular, the individuals who evaluate maternal participant safety prior to unblinding maternal participants at the 1-month postdelivery visit will be blinded.

Because the BNT162 RNA-based COVID-19 vaccine candidate and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the maternal study participants from identifying the study intervention type based on its appearance during the blinded portion of the study.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any maternal study participants prior to the maternal participant being unblinded. Contact between the unblinded dispenser and blinded maternal study participants and unblinded administrator and blinded maternal study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments until the maternal participant is unblinded at the 1-month post delivery visit.

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.

6.3.4. Blinding of the Sponsor

The study team will be unblinded to the participant's study intervention allocation when maternal participants complete the 1-month postdelivery visit. Prior to unblinding the maternal participants at the 1-month postdelivery visit the majority of sponsor staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded (further details will be provided in a data blinding plan):

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

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

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), and a medical monitor and/or a clinical scientist who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.4).

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team.

6.3.5. 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 maternal participant's vaccine assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a maternal participant's vaccine assignment unless this could delay further management of the participant.

If a maternal participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

Instructions on how to unblind participants ahead of administration of BNT162b2 to placebo recipients will be provided separately: this unblinding will NOT be performed in the IRT.

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

6.5.1. Prohibited During the Study – Maternal Participants

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

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 14 days before and 7 days after each study vaccination, including seasonal and pandemic influenza vaccines.
- Receipt of chronic systemic treatment with known immunosuppressant medications 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 Visit 3
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.
- Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.
- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a maternal participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study – Maternal Participants

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

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

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

6.5.3. Recording Nonstudy Vaccinations and Concomitant Medications – Maternal Participants

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

- All vaccinations received from 14 days prior to study enrollment until the 6-month follow-up visit for participants originally randomized to receive BNT162b2.

- Any medication taken to treat AEs from the signing of the ICD through the final study visit be recorded in the CRF.

- Prohibited medications listed in Section 6.5.1 will be recorded in the CRF, to include start and stop dates, name of the medication, dose, unit, route, and frequency from the signing of the ICD through the final study visit.

6.5.4. Prohibited During the Study – Infant Participants

- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.

6.5.5. Permitted During the Study – Infant Participants

- ONLY routine treatments, routine vaccinations, and routine procedures (eg, circumcision) are permitted at any time during the study, in accordance with national recommendations, medical standard of care, or accepted practice.

- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during infant participant participation in the study.

- Local anesthetic may be applied to the site of the blood draw, as appropriate.

6.5.6. Recording Concomitant Medications – Infant Participants

The following concomitant medications will be recorded in the CRF:

- Any medications taken to treat AEs and/or SAEs from Visit 1 through the final study visit.

6.6. Dose Modification

Dose modification is not applicable in this study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

A maternal participant may withdraw from the study at any time at her own request or the infant participant may be withdrawn at any time at the request of his/her parent(s). Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Maternal 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, she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with her. 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 postvaccination study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A maternal participant will be considered lost to follow-up if 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 return for scheduled visits and is unable to be contacted by the study site:

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

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

- Should the participant continue to be unreachable, 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.

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

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

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 maternal participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all maternal participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the maternal participant's routine clinical management and obtained before signing of the ICD may be utilized for baseline and/or screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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 in this study is dependent on when a maternal participant is enrolled and which vaccine she is given while pregnant. It is expected that most maternal participants will have to give up to 6 blood samples (20 mL each).

Additionally, 20 mL of blood for maternal participants will be taken at an unplanned convalescent visit at any time a maternal participant develops respiratory symptoms indicating a potential COVID-19 infection. Maternal participants would therefore have a total blood sampling volume of approximately up to 140 mL during the study period. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days. Approximately 10 mL of cord blood will be taken from each infant participant; if cord blood is unavailable, a blood sample of up to 5 mL (based on weight) will be collected. A 5-mL blood sample will be collected from each infant at the 6-month postdelivery visit; in addition, a blood sample of up to 5 mL will be collected at each convalescent illness visit.

8.1. Efficacy and/or Immunogenicity Assessments

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

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

8.1.1. Maternal Participants

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

Confirmed COVID-19, first definition: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;

- Vomiting.

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

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

Confirmed Severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths/min, HR ≥125 beats/min, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional outcomes defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html):

- Hospitalization;
- Admission to the ICU;
- Intubation or mechanical ventilation;
- Death.

8.1.2. Infant Participants

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the **infant participant**; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness). Signs and symptoms of an acute respiratory illness will not be considered a potential COVID-19–related illness if they occur within the first 72 hours after birth.

Confirmed COVID-19, first definition: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Diarrhea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) but does not trigger a potential COVID-19 illness visit unless, in the opinion of PI, it is deemed necessary:

- Nasal congestion or runny nose;
- Poor appetite or poor feeding;
- Abdominal pain (colic).

Confirmed Severe Infant COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness:
  - RR (breaths/min): >50 from birth to 1 week of age, ≥40 from 1 week to 1 month of age, ≥34 from 1 month to 6 months of age;
  - HR (beats/min): >180;
  - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg[24];

- Respiratory failure (defined as needing high-flow oxygen including nasal CPaP/BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg) (<5th percentile for age):
    - <65 from birth to 1 week of age, <75 from 1 week to 1 month of age, <100 from 1 month to 6 months of age;

OR

  - Requiring vasoactive drugs to maintain BP in the normal range;
- Significant acute renal failure: serum creatinine >2 times ULN for age or 2-fold increase in baseline creatinine;
- Significant GI/hepatic failure: total bilirubin >4 mg/dL or ALT 2 times ULN for age;
- Significant neurologic dysfunction: Glasgow Coma Scale score <11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline;
- Admission to an ICU;
- Death.

Confirmed Multisystem Inflammatory Syndrome in Children (MIS-C) definition[25]:
as per the CDC MIS-C case definition:

- An infant presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
  - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
  - Renal (eg, acute kidney injury or renal failure);
  - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);

- Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
- GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
- Dermatologic (eg, rash, mucocutaneous lesions);
- Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND

- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR
- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

The following are applicable for both maternal and infant participants:

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

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

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: a positive N-binding antibody result in a participant with a prior negative N-binding antibody result.

8.1.3. Immunogenicity

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

- SARS-CoV-2 neutralization assay
- Full-length S-binding IgG levels
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the **central laboratory**.

8.1.4. Total Volume of Blood Collected – Maternal Participants

The total volume of blood collected for antibody assessment over the course of the study will be up to approximately 120 mL (~20 mL/visit) and an additional 20 mL during each unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection.

8.1.5. Total Volume of Blood Collected – Infant Participants

Blood samples will be collected according to the directive 2001/20/EC: Ethical considerations for clinical trials on medicinal products conducted with minors.[26]

All infants will have a cord blood sample collected at birth. The total volume of cord blood to be collected for antibody assessment in this study will be approximately 10 mL.

If cord blood is unavailable, a blood sample may be collected from the infant participant up to 72 hours after birth but preferably within 24 hours after birth. The infant's weight must be used to determine the volume of blood that can be collected (see Table 1).

The maximum volume of blood collected from the infant in the absence of cord blood will be no more than 5 mL at planned study visits (based on weight). An additional sample of up to 5 mL may be collected during each unplanned convalescent visit at any time an infant participant develops respiratory symptoms indicating a potential COVID-19 infection.

Table 1. Guideline for Infant Blood Draw, if Cord Blood Sample Was Not Obtained

Body Weight (in kg)	Approximate Volume of Blood (in mL) to Be Collected
<1.3	No blood draw
1.3 - ≤2.4	1.0
>2.4 - ≤3.7	2.0
>3.7 - ≤4.9	3.0
>4.9 - ≤6.2	4.0
>6.2	5.0

8.1.6. Biological Samples

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

The maternal participant may request that her or her infant's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA 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 maternal participants at the first visit to establish a baseline. Significant medical history and observations from any physical examination 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 vaccination will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever) and use of antipyretic medication that occur in the 7 days after administration of the study intervention, where Day 1 is the day of vaccination. Reactogenicity will not be collected in the e-diary for placebo recipients who subsequently receive BNT162b2 1 month following delivery. These prospectively self-reported occurrences of local reactions and systemic events are graded as described in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments

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

8.2.2. Electronic Diary

Maternal participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the maternal participant's own personal device. Maternal participants will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention, where Day 1 is the day of vaccination. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions, systemic events, and antipyretic medication usage 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.

Maternal participants originally randomized to placebo who subsequently receive BNT162b2 1 month following delivery, will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with Section 8.3.2.

If the maternal participant lives in an area with poor network connection (certain countries only), a study staff/field worker may visit the maternal participant in her home or contact her via phone daily after vaccination to assess and record local reactions, systemic events, and temperature each day (beginning in the morning) for 6 days following vaccination (Day 2 through Day 7) where this system of follow-up is well established. Maternal participants may call the site and report additional local reactions and systemic events at any time during the Day 1 through Day 7 reporting period. The study staff/field worker will be required to record these data on a provisioned device or an application on a personal device, thus providing the accurate representation of the maternal participant's experience at that time. For events persisting on Day 7 and use of antipyretic medication continuing on Day 7, the field worker will continue to visit the participant and record information until resolution.

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

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

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

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[21]

8.2.2.2. Local Reactions

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

Redness and swelling will be measured and recorded by the maternal participants/study staff member/field worker 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.

Where appropriate, the site staff/field worker will educate the maternal participant regarding signs and symptoms that would prompt site contact.

Table 2. Local Reaction Grading Scale

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

8.2.2.3. Systemic Events

Prior to vaccination on Day 1, a baseline assessment of fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain will be recorded in the e-diary.

During the reactogenicity e-diary reporting period, maternal participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. Based on local practice in certain countries/locales, a study staff member/field worker will call or visit maternal participants daily after vaccination to assess the presence of systemic events during the reactogenicity reporting period. The symptoms will be assessed by the maternal participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

Maternal participants will also be instructed to contact site staff if they visit the emergency room or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain within 7 days after vaccination. Based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant. The study staff/field worker may also contact the maternal participant to obtain additional information on events entered into the e-diary.

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 maternal participant's systemic event as Grade 4. If a maternal 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 maternal participant.

Table 3. Systemic Event Grading Scale

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

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to maternal 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. Similarly, based on local practice in certain countries/locales, the study staff/field worker will call or visit maternal participants daily during the reactogenicity reporting period to collect the temperature.

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

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a maternal participant's fever as >40.0°C (>104.0°F). If a maternal 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 maternal participant.

Table 4. Scale for Fever

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

8.2.2.5. Antipyretic Medication

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

8.2.3. Stopping Rules

The following stopping rules are in place for all Phase 2 maternal participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 3. Stopping rules do not apply to maternal participants who initially received placebo and subsequently receive BNT162b2. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

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

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for participants receiving the first dose. Maternal participants scheduled to receive Dose 2 at the time of a study pause may proceed with vaccination.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162b2; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

Stopping Rule Criteria:

1. If any participant vaccinated with BNT162b2 develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
2. If any participant vaccinated with BNT162b2 develops a Grade 4 local reaction or systemic event after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with BNT162b2 develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with BNT162b2 report the same or similar severe (Grade 3) AE after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

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

6. If any participant vaccinated with BNT162b2 experiences any of the following within 7 days after vaccination, where Day 1 is the day of vaccination: severe vaginal bleeding (eg, partial abruption); severe preeclampsia; eclampsia; HELLP syndrome; life-threatening sequelae of preeclampsia (eg, pulmonary edema); stillbirth; or fetal loss.

7. If ≥2 maternal participants vaccinated with BNT162b2 experience premature delivery or preterm premature rupture of membranes within 14 days after vaccination.

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

The unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular, greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death.

Observed rates of these indicators will be compared with what could be expected in a population similar to the study participants based upon available information at the time of review.

8.2.5. Clinical Safety Laboratory Assessments

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 2.

AEs will be reported by the maternal participant (or the parent[s] for the infant participant).

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

Each maternal participant and parent of the infant 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.

The procedures described in this section pertain to both the infant participant and maternal participant, unless otherwise indicated.

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 maternal participant including her fetus begins from the time the maternal participant provides informed consent, which is obtained before participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

In this study, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 4.

From Visit 4 through Visit 8, SAEs will be collected for maternal participants originally randomized to BNT162b2. In addition, AEs occurring up to 48 hours after blood draws and collection of nasal swabs that are related to study procedures must be reported in the CRF.

Additionally, for those maternal participants who originally received placebo but go on to receive BNT162b2 at Visit 101 and Visit 102, AEs and SAEs will be collected through and 1 month after the second dose of BNT162b2 (Visit 103).

For the infant participant, the time period for actively eliciting and collecting nonserious AEs ("active collection period") begins at birth and continues through and including 1 month after birth. SAEs and AESIs will be collected from birth through and including 6 months of age.

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

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

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

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

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

Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition (Section 8.1) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

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, if applicable, immediately upon awareness and under no circumstance should this exceed 24 hours.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death defined as those that occur within 1 month of birth, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs. In addition, infant deaths after 1 month of age should be reported as SAEs.

Further follow-up may be requested by the sponsor and will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

SAEs occurring in the mother after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study intervention must be reported to Pfizer Safety.

For those SAEs or deaths that occur to the infant after the active collection period should be reported when the investigator believes the SAE or death has at least a reasonable possibility of being related to study intervention.

8.3.1.2. Recording Nonserious AEs and SAEs in 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.

The investigator obtains general information on the pregnancy and its outcome for all study participants. The investigator will follow the pregnancy until completion (or until pregnancy termination). 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).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death defined as those deaths that occur within 1 month of birth, or congenital anomaly (in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

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 2.

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

8.3.3. Follow-up of AEs and SAEs

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

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

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Additional Exposure Scenarios That May Result From the Exposure to the Study Intervention

8.3.5.1. Environmental Exposure During Pregnancy

Environmental exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include HCPs, family members, and other roles that are involved in the trial participant's care.

Note: This does NOT apply to maternal participants enrolled in this trial.

- The scenarios below describe environmental exposures that could lead to an EDP:
    - A female is found to be pregnant while being exposed or having been exposed to study intervention by environmental exposure. Below are some examples:
        - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inadvertent product administration via needlestick.
        - A male family member or healthcare provider who has been exposed to the study intervention 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 investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy). 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 [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), 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).

8.3.5.2. Exposure During Breastfeeding

Exposure-during-breastfeeding reports are not expected for maternal participants who breastfeed a child delivered during the study.

Environmental exposure during breastfeeding occurs when a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention (eg, 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

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

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

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

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

> The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.
>
> OR
>
> The investigator considers that there is a reasonable possibility that the event was related to study intervention.

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

8.3.8. Adverse Events of Special Interest

This section provides information on AESIs that may be detected during the study.

For Infant Participants:

- Major congenital anomaly
- Developmental delay

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.

8.3.8.1. Lack of Efficacy

This section is not applicable, as efficacy is yet to be demonstrated in the study population.

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.

Other 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.

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**.

Other examples include, but are not limited to:

- 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.

8.4. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

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

8.11. Study Procedures – Maternal Participants

The following procedures apply to both Phase 2 and Phase 3 maternal participants.

8.11.1. Visit 1: Screening (-28 Days to Vaccination 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the maternal 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 maternal participant. The source data must reflect that the informed consent was obtained before participation in the study.

Standard-of-care procedures performed prior to informed consent can be considered for use in the study provided they follow guidance around the timing of procedures stipulated in the protocol.

In countries/locales where procedures to confirm maternal participant eligibility for this clinical trial are not routinely performed, the procedures must be obtained and reviewed by the investigator or qualified designee up to 28 days prior to vaccination.

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

The following procedures will be performed:

- Obtain and record the participant demography (including complete date of birth [dd-Mmm-YYYY], sex, race, racial designation, and ethnicity). The date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record current alcohol and tobacco usage.
- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Obtain and record the LMP and EDD.
- Measure and record vital signs, including oral temperature, seated blood pressure, and heart rate.
- Perform physical examination including but not limited to weight and height, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Perform obstetric examination including but not limited to fetal heart tones and fetal movement. Note: Repeat and conduct targeted physical and obstetric examination if it was last performed greater than 7 days prior to vaccination.
- Perform an obstetric ultrasound scan and/or record findings to confirm singleton pregnancy and rule out fetal abnormalities.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- 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.
- Explain the e-diary technologies available for this study (see Section 8.14) and assist the participant in downloading the study application onto her own device or issue a provisioned device if required.
- Record systemic events at baseline in the e-diary.
- Assign a single participant identifier using the IRT system.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination, OR explain to the maternal participant that a study staff member/field worker will call or visit her every day from Day 2 through Day 7 after vaccination (where Day 1 is the day of vaccination) to collect or take her temperature and record systemic events, acute local reactions, and use of antipyretic medication in a diary (if applicable).

- Provide instructions on COVID-19 illness e-diary completion and ask the participant to complete the COVID-19 illness e-diary at least weekly, if she is diagnosed with COVID-19 or has possible new or increased symptoms, or when she receives a reminder. See Section 8.14 for further details.

- Ask the participant to contact the site staff or investigator immediately if she experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit or COVID-19 illness visit is required:

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

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

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any respiratory symptoms as detailed in Section 8.13.

- Record AEs and SAEs as described in Section 8.3.

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

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

- Complete the source documents.

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

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

8.11.1.1. Visit 2 – Vaccination 2 (Clinic: 19-23 Days After Vaccination 1)

If delivery occurs before this visit, this visit will be conducted as soon as possible after delivery. It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Measure vital signs (body temperature, pulse rate, and seated blood pressure).
- Perform targeted physical examination evaluating/noting any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Significant medical and surgical history and abnormal observations from the physical examination will be documented and recorded in the CRF.
- Perform obstetric examination including but not limited to fetal heart tones and fetal movement.
- Record AEs and SAEs as described in Section 8.3.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- Ensure and document that the participant is still eligible for continued participation.
- Ensure that the maternal participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
  Note: blood samples for immunogenicity will be drawn in Phase 2 maternal participants only.
- Obtain a nasal swab (collected by site staff).

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

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

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

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

  - Fever ≥39.0°C (≥102.1°F).

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

  - Severe pain at the injection site.

  - Any severe systemic event.

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

- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any COVID-19 illness symptoms as detailed in Section 8.13.

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

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

- Complete the source documents.

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

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

8.11.1.2. Visit 3 – 2-Week Postvaccination Follow-up (Clinic)

If delivery occurs before this visit, this visit will not be conducted.

- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- 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.
- Ensure and document that the participant is still eligible for continued participation.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record AEs and SAEs as described in Section 8.3.
- Ask the participant to contact the site staff or investigator if an emergency room visit or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any COVID-19 illness symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.3. Visit 4 – 1-Month Postvaccination Follow-up Visit (Clinic: 28-35 Days After Visit 2)

If delivery occurs before this visit, this visit will not be conducted.

- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure).
- Perform targeted physical examination evaluating/noting any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Significant medical and surgical history and abnormal observations from the physical examination will be documented and recorded in the CRF.
- Perform obstetric examination including but not limited to fetal heart tones and fetal movement.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with an AE.
- Ensure and document that the participant is still eligible for continued participation. Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record AEs and SAEs as described in Section 8.3.
- Ask the participant to contact the site staff or investigator if an emergency room visit or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any COVID-19 illness symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.4. Visit 5 – Delivery

The delivery visit spans the time from when a participant is admitted in labor through discharge following delivery of her infant. Protocol-specified procedures associated with this delivery visit may be done at any time during this period.

- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- Ensure and document that the participant is still eligible for continued participation.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing. If a sample for this purpose has already been collected in the previous 7 days (eg, per the procedures at Visit 4 for Phase 2/3 participants), a second sample need not be collected.
    - Note: A cord blood sample of approximately 10 mL for immunogenicity assessments must also be collected. Please refer to Section 8.17.1 for details of the infant delivery visit.
- Record pregnancy outcome information, including vital status of the infant (live, stillbirth, etc), mode of delivery (vaginal delivery or cesarean delivery), and the use of any assisted devices (forceps or vacuum).
- Record AEs and SAEs as described in Section 8.3.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any COVID-19 illness symptoms as detailed in Section 8.13.
- Schedule a telephone call for the participant's next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.5. Visit 6 – 1-Week Postdelivery Follow-up (Telephone Call: 7-10 Days After Delivery)

- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- Ensure and document that the participant is still eligible for continued participation.
- If not obtained at the time of delivery, record pregnancy outcome information, including vital status of the infant (live, stillbirth, etc), mode of delivery (vaginal delivery or cesarean delivery), and the use of any assisted devices (forceps or vacuum).
- Record AEs and SAEs as described in Section 8.3.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any COVID-19 illness symptoms as detailed in Section 8.13.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.6. Visit 7 – 1-Month Postdelivery Follow-up (Clinic: 21 to 35 Days After Delivery)

- All participants will be unblinded. Maternal participants who received BNT162b2 will follow the procedures below and those who received placebo will follow the procedures in Section 8.16.
- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- Ensure and document that the participant is still eligible for continued participation.
- Record AEs and SAEs as described in Section 8.3.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if she experiences any COVID-19 illness symptoms as detailed in Section 8.13.

- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.7. Visit 8 – 6-Month Postdelivery Follow-up (Clinic: 160-200 Days After Delivery)

- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).
- Record nonstudy vaccinations as described in Section 6.5.
- Collect and record concomitant medication associated with AE/SAEs.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record SAEs as described in Section 8.3.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.12. Unscheduled Visit for Reactogenicity Events

If a Grade 3 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (≥39.0°C [102.1°F]) (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Section 8.2.2.2), systemic event (Section 8.2.2.3), or fever (>40.0°C [>104.0°F]) (Section 8.2.2.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm the fever and whether the event meets the criteria for Grade 4.

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

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

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

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

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

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.2.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.2.3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

8.13. COVID-19 Surveillance (All Maternal Participants)

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

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

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's

opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Maternal participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

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

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

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

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

- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:

- Symptoms and signs, including

    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths/min, HR ≥125 beats/min, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)

    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

    - Significant acute renal, hepatic, or neurologic dysfunction

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

    - Clinical diagnosis

    - Local laboratory SARS-CoV-2 test result(s)

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

    - Full blood count

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

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

    - Hospitalization

- Admission to the ICU
- Death

- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the maternal participant is maintained to ensure that endpoint events are not missed for her or her infant. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant and the study site staff will be established. The participant may be able to utilize her own devices to access this technology, or use a device provided by the sponsor.

Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a maternal participant is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory–generated positive results from the Visit 1 and Visit 2 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 2; therefore, Vaccination 2 should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test) diagnosed at Visit 1 or any time between Visit 1 and Visit 2 does not meet exclusion criterion 2; therefore, Vaccination 2 should proceed as normal.

8.16. Procedures for Administration of BNT162b2 to Those Originally Assigned to Placebo

Maternal participants will be given BNT162b2 at the 1-month postdelivery visit, and will follow the procedures listed in this section for the remainder of their participation in the study.

8.16.1. Visit 101 – Vaccination 3 – 1-Month Postdelivery Follow-up (Clinic: 21 to 35 Days After Delivery)

- Confirm that the participant originally received only placebo at Vaccination 1/2. Secondary confirmation by another site staff member is required.

- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since their last visit (if any).

- Before vaccination and before any study-related procedures are performed: Review and consider inclusion criteria 2, 5, and 11 and exclusion criteria 1, 3, 4, 5, 9, 13, 14, 15, and 17 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

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

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

- Record AEs as described in Section 8.3.

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.

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

- Obtain the participant's vaccine vial allocation using the IRT system.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2 into the deltoid muscle of the (preferably) nondominant arm.

- Site staff must observe the participant for at least 30 minutes after BNT162b2 administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

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

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

- Complete the source documents.

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

8.16.2. Visit 102 – Vaccination 4 (19 to 23 Days After Visit 101)

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

- Record AEs as described in Section 8.3.

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

- Before vaccination and before any study-related procedures are performed: Review and consider inclusion criteria 2, 5, and 11 and exclusion criteria 1, 3, 4, 5, 9, 13, 14, 15, and 17 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

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

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

- Obtain the participant's vaccine vial allocation using the IRT system.

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

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

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment to call the participant by telephone for the next study contact.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the dispenser/administrator updates the study intervention accountability records.

8.16.3. Visit 103 – 1-Month Follow-up Telephone Contact (After Vaccination 4) (28 to 35 Days After Visit 102)

- Contact the participant by telephone.
- Record AEs as described in Section 8.3.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for her clinical care.
- Phase 3 only: For participants who are HIV-infected, record HIV viral load and CD4 count results from the most recent test performed since Visit 101 (if any).
- Ask the participant to contact the site staff or investigator if 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.

8.17. Study Procedures – Infant Participants

8.17.1. Infant Participants: Visit 1 – Delivery

- Manually assign a single infant participant identifier. This will be assigned manually by the site using the following convention: the infant participant's identifier will be the maternal participant's IRT-generated numeric ID but with the fifth digit changed to a 2 (eg, if the maternal participant is given number 10011001, then the infant will be 10012001).
- Collect demography (including complete date of birth [ie, dd-Mmm-YYYY], sex, race, and ethnicity). The date of birth will be collected to critically evaluate the immune response.
- Measure vital signs, including temperature, heart rate, oxygen saturation by pulse oximetry, and respiratory rate.

- Standard-of-care vital signs and examination procedures can be considered for use in the study provided they were performed within 48 hours after birth. Note: Please reference the physical examination procedures below for details.

- Perform a physical examination, if not performed as part of standard of care, noting any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; back; musculoskeletal; extremities; genitourinary; neurological; and lymph nodes. Abnormal results must be recorded on source documents as well as the physical examination pages of the CRF; only if the abnormal finding is deemed to be clinically significant should this be recorded on the AE pages of the CRF.

- Collect and record concomitant medication associated with AE/SAEs.

- Ensure and document that the infant is eligible.

- Collect a cord blood sample of approximately 10 mL for immunogenicity assessments. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord and after the umbilical cord has been clamped and cut.

- If cord blood is unavailable, a blood sample may be collected from the infant participant preferably within 72 hours. The volume of blood collected will be based on the weight of the infant (refer to Table 1).

- Record AEs, SAEs, and AESIs as described in Section 8.3.

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

- Ask the maternal participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the infant participant experiences any COVID-19 illness symptoms as detailed in Section 8.18.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.17.2. Visit 2 – 1-Week Postdelivery Follow-up (Telephone Call: 7-10 Days After Visit 1)

- Ensure and document that the infant is still eligible.

- Record breastfeeding information.

- Collect and record concomitant medication associated with AE/SAEs.

- Record AEs, SAEs, and AESIs as described in Section 8.3.
- Schedule an appointment for the participant to return for the next study visit.
- Ask the maternal participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the infant participant experiences any COVID-19 illness symptoms as detailed in Section 8.18.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.17.3. Visit 3 – 6-Months-of-Age Follow-up (Clinic: 160-200 Days After Visit 1)

- Record concomitant medication associated with SAEs.
- Record breastfeeding information.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing. The volume of blood collected will be based on the weight of the infant (refer to Table 1).
- Record AEs, SAEs, and AESIs as described in Section 8.3.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.18. COVID-19 Surveillance (All Infant Participants)

If an infant participant experiences any of the following (irrespective of perceived etiology or clinical significance), the maternal participant is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days after symptom onset (and at the latest 4 days after symptom resolution).
Note that this does not substitute for an infant participant's routine medical care. Therefore, maternal participants should be encouraged to seek care, if appropriate, from their infant's usual provider.

Additionally:

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

Signs and symptoms of an acute respiratory illness in the infant will not be considered a potential COVID-19–related illness if they occur within the first 72 hours after birth and should not trigger an illness visit.

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

8.18.1. Potential Infant COVID-19/MIS-C Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

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

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in Section 6.5.1 received by the participant if required for his/her clinical care.
- If the visit is conducted in person, obtain a nasal swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the maternal participant to collect a nasal swab from the infant and ship for assessment at the central laboratory.

- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
  - Clinical signs at rest indicative of severe systemic illness:
    - RR (breaths/min): >50 in birth to 1 week of age, ≥40 in 1 week to 1 month of age, ≥34 in 1 month to 6 months of age
    - HR (beats/min): >180
    - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92% or PaO_2/FiO_2 <300 mm Hg;
    - Respiratory failure (defined as needing high-flow oxygen including nasal CPaP/BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
    - Evidence of shock or cardiac failure;
    - SBP (mm Hg):
    - <65 from birth to 1 week of age, <75 from 1 week to 1 month of age, <100 from 1 month to 6 months of age;

    OR

    - Requiring vasoactive drugs to maintain BP in the normal range;
    - Significant acute renal failure: serum creatinine >2 times ULN for age or 2-fold increase in baseline creatinine;
    - Significant GI/hepatic failure: total bilirubin >4 mg/dL or ALT 2 times ULN for age;
    - Significant neurologic dysfunction: Glasgow Coma Scale score <11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline;
    - Admission to an ICU;
    - Death;
    - Clinical diagnosis;

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

- Full blood count, blood chemistry, specifically creatinine, urea, liver function tests, and CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6 if available.

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

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

- Record AEs, as appropriate as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

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

- Collect a blood sample (up to 5 mL based on weight [Table 1]) for immunogenicity testing.

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

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. Estimands and Statistical Hypotheses

9.1.1. Estimands

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

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.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (Section 9.3). These estimands estimate the vaccine effect in the hypothetical settings where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on the evaluable efficacy populations (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by the all-available efficacy (mITT) populations. Missing laboratory results will not be imputed.

9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Immunogenicity

The primary objectives of the study are to evaluate immunobridging of the immune response to prophylactic BNT162b2 one month after Dose 2 in pregnant women compared to nonpregnant women. The assessment of immunobridging is based on testing the hypothesis:

$$H_0: \ln(\mu_{pregnant}) - \ln(\mu_{nonpregnant}) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_{pregnant}) - \ln(\mu_{nonpregnant}) > \ln(0.67)$$

where $\ln(0.67)$ corresponds to a 1.5-fold margin for immunobridging, and $\ln(\mu_{pregnant})$ and $\ln(\mu_{nonpregnant})$ are the natural log of the geometric means for SARS-CoV-2 neutralizing titers at 1 month after Dose 2 from the pregnant group and nonpregnant group. The pregnant group is a subset of maternal participants who receive BNT162b2 from this study, and the comparator is randomly selected from the nonpregnant female participants from Study C4591001 who received BNT162b2 and are within the same age group.

Immunobridging success will be declared if the lower bound of the 2-sided 95% CI for the ratio of GMTs (pregnant over nonpregnant) is greater than 0.67 (1.5-fold margin).

The immunobridging hypotheses will be assessed sequentially, for participants without prior infection first, and then for participants with or without prior infection, to control the overall type I error to the desired level of 2.5% (1-sided).

9.1.2.2. Statistical Hypothesis Evaluation for Vaccine Efficacy

The secondary endpoints are to evaluate VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior infection, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination. The assessment of VE will be based on testing the hypothesis:

$$H_0: VE \leq 0\% \text{ vs } H_1: VE > 0\%$$

for VE_1 and VE_2, respectively.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%.

The VE will be assessed for participants without prior infection first, and then for participants with or without prior infection.

9.1.3. Multiplicity Consideration

The fixed sequential testing procedure will be used for multiplicity control. For the immunobridging assessments of immune response to prophylactic BNT162b2 in pregnant women compared to nonpregnant women, the immunobridging in participants without evidence of prior SARS-CoV-2 infection will be assessed first. The immunobridging in participants with or without prior infection will be assessed only if success is declared for the first immunobridging assessment. Both hypothesis tests will be conducted at a significance level of 1-sided 0.025. This controls the overall type I error at the desired level of 2.5%. If the required number of confirmed COVID-19 cases is accrued, the VE endpoints will be evaluated sequentially in a similar way to control the overall type I error rate.

9.2. Sample Size Determination

The sample size for the Phase 2 portion of the study and for the entire study is not driven by statistical hypothesis testing.

The first 295 participants who received BNT162b2 from this study and a random sample of 295 female participants 18 to 55 years of age from the Phase 3 C4591001 trial who received BNT162b2 will be the immunogenicity subset for the immunobridging assessments. Assuming a 10% nonevaluable rate and that an additional 10% of participants have prior infection, approximately 239 evaluable participants in each comparison group will be included in the immunobridging assessment based on the participants without evidence of infection prior to vaccination. Approximately 265 evaluable participants in each comparison group will be included in the immunobridging assessment based on participants with and without evidence of prior infection.

With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 239 evaluable participants per group will provide a power of 92.0% to declare success for the immunobridging of pregnant women to nonpregnant women without evidence of prior SARS-CoV-2 infection, in terms of neutralizing antibody GMR, 1 month after Dose 2 (see Table 5). For the comparison based on participants with and without evidence of prior infection, an evaluable sample size of 265 participants per group will provide a power of 90.1% to declare immunobridging success (see Table 5).

Table 5. Power Analysis for Immunobridging Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Group	Power[b]
Lower limit of 95% CI for GMR (pregnant/nonpregnant without evidence of prevaccination infection) >0.67	0.65	-0.2	239	92.0%
Lower limit of 95% CI for GMR (pregnant/nonpregnant with and without evidence of prevaccination infection) >0.67	0.71	-0.2	265	90.1%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.

a. The assumptions of standard deviation were based on the 1-month post–Dose 2 immunogenicity results from C4591001 Phase 2, 18- to 55-year age group, evaluable immunogenicity population with negative baseline SARS-CoV-2 (without past infection) and all-available population (with and without past infection).
b. At a 0.05 alpha level (2-sided).

Assuming 15% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, a 1.3% annual attack rate, and a true VE of 90%, a total of approximately 6 first confirmed COVID-19 illness cases are expected within 1 month after delivery. This provides approximately 56.4% power to conclude true VE >0% (Table 6). Dependent upon the evolution of the pandemic, the COVID-19 attack rate observed in this study may be higher or lower. Since it requires at least 12 cases to achieve 90% power, the hypothesis test will be conducted only if at least 12 cases have accrued.

Table 6. Power for Vaccine Efficacy Assessment

Power	Total Cases	Case Split[a] to Claim Success[b] (VE%)
56.4%	6	0:6 (100%)
80.6%	9	1:8 (87.5%)
77.1%	10	1:9 (88.9%)
73.6%	11	1:10 (90%)
91.1%	**12**	**2:10 (80%)**

Abbreviation: VE = vaccine efficacy.

a. Case split numbers represent the number of cases in the active vaccine group vs the number of cases in the placebo group.
b. Success criteria: lower bound of 95% CI for VE > 0%.

For safety outcomes, Table 7 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, with 175 participants in a vaccine group, there is 83% probability of observing at least 1 AE.

Table 7. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=175	N=2000
0.01%	0.02	0.18
0.05%	0.08	0.63
0.10%	0.16	0.86
0.20%	0.30	0.98
0.50%	0.58	>0.99
1.00%	0.83	>0.99
2.00%	0.97	>0.99
5.00%	>0.99	>0.99

Note: N = number of participants in a vaccine group.

9.3. Analysis Sets

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

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity (maternal)	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 1 evaluable immunogenicity (maternal)	All eligible randomized participants who receive Dose 1 of the vaccine to which they are randomized, have at least 1 valid and determinate immunogenicity result from the blood sample collected after Dose 1 and before Dose 2, and have no other important protocol deviations before Dose 2 as determined by the clinician.
Evaluable immunogenicity (infant)	All infant participants born to evaluable immunogenicity maternal participants.
All-available immunogenicity (maternal)	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
All-available immunogenicity (infant)	All infant participants born to all-available immunogenicity maternal participants.
Evaluable efficacy (maternal)	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.

Population	Description
All-available efficacy (mITT) (maternal)	Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination. Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses.
All-available efficacy (mITT) (infant)	All infant participants born to Dose 1 all-available maternal participants.
Safety (maternal)	All randomized participants who receive at least 1 dose of the study intervention.
Safety (infant)	All infant participants born to maternal participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

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

9.4.1. 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 (or their mothers) actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity populations. An additional analysis may be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they (or their mothers) were randomized. Missing serology data will not be imputed.

9.4.1.1. Analyses for Binary Data

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

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

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

9.4.1.2. Analyses for Continuous Data

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

9.4.1.2.1. Geometric Means

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

9.4.1.2.2. 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 neutralization titers or antibody levels (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs are obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.4.1.2.3. Geometric Mean Ratios

Model-based

As the primary approach, the GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model.

Unadjusted

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers in pregnant women minus that in nonpregnant women) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.4.1.2.4. Reverse Cumulative Distribution Curves

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

9.4.2. Primary Endpoint(s)

Endpoint	Statistical Analysis Methods
Safety (maternal participants)	Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination (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 9.4.1.1). AEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs from Dose 1 to 1 month after Dose 2 will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. Analysis methods are described in Section 9.4.1.1. SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 through 1 month after delivery will be provided for each vaccine group. AEs and SAEs reported for maternal participants during the open-label follow-up period will be summarized separately.
Immunogenicity in participants without evidence of prior SARS-CoV-2 infection (maternal participants)	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in pregnant women to nonpregnant women 1 month after Dose 2 will be provided along with associated 2-sided 95% CIs (see Section 9.4.1.2.3). Only participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection will be included in the analysis. Immunobridging success 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 this immunobridging assessment, a linear regression model that includes terms for age and group (pregnant vs nonpregnant) will be used to calculate the adjusted GMR and 2-sided 95% CI. The unadjusted GMR and CI will also be calculated.
Immunogenicity in participants with and without evidence of prior SARS-CoV-2 infection (maternal participants)	This endpoint will be analyzed the same way as for the participants without evidence of infection, except that the linear regression model will also include the infection status. Both model-based and unadjusted GMR and 2-sided 95% CI will be provided. The immunobridging assessment will be performed only if success is declared for the immunobridging in participants without infection.

9.4.3. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Vaccine efficacy	**Ratio of confirmed COVID-19 illness from 7 days after Dose 2 through 1 month after delivery per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of first confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after Dose 2. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method. The hypothesis test will be performed if at least 12 cases are accrued at the time of analyses. **Ratio of confirmed COVID-19 illness from 7 days after Dose 2 through 1 month after delivery per 1000 person-years of blinded follow-up in maternal participants with and without evidence of infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group** The same analysis method used for the first VE endpoint will be applied. The hypothesis test for this VE objective will be performed if the above VE objective is met. **Ratio of incidence of asymptomatic infection of SARS-CoV-2 in evaluable participants without evidence of prior SARS-CoV-2 infection for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method. The analyses will be based on the evaluable efficacy population and the all-available efficacy population. Missing efficacy data will not be imputed.
Immunogenicity (maternal participants)	**GMTs/GMCs of SARS-CoV-2 neutralizing titers and full-length S-binding IgG levels at baseline, 2 weeks after Dose 2, 1 month after Dose 2, and 6 months after delivery** For SARS-CoV-2 neutralizing titers and full-length S-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each vaccine group before vaccination and at each subsequent time point after vaccination. Statistical methods are described in Section 9.4.1.2.1. Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers (Section 9.4.1.2.4). **GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding IgG levels from before vaccination through 2 weeks after Dose 2, 1 month after Dose 2, and 6 months after delivery** For SARS-CoV-2 neutralizing titers and full-length S-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each vaccine group from before vaccination to each subsequent time point after vaccination.

Endpoint	Statistical Analysis Methods
	GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The statistical methods are described in Section 9.4.1.2.2.
Safety (infant participants)	Counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with specific birth outcomes, AEs from birth through 1 month of age, and SAEs and AESIs through 6 months of age will be provided by vaccine group according to the study intervention the maternal participants received. A 3-tier approach will be used to summarize AEs.
Immunogenicity (infant participants)	GMCs at birth and 6 months after delivery, and GMFRs for full-length S-binding IgG levels, will be summarized for infant participants using the same statistical analysis method described for the secondary immunogenicity endpoints for maternal participants.

9.4.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
COVID-19 incidence rate (maternal participants)	Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness from 7 days after the second dose of BNT162b2 will be provided for participants who received BNT162b2 at initial randomization and at 1 month after delivery, respectively.
Asymptomatic SARS-CoV-2 infection (maternal participants)	Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic SARS-CoV-2 infection based on the N-binding antibody seroconversion for participants who received BNT162b2 at initial randomization and have no serological or virological evidence of prior SARS-CoV-2 infection.
Serological responses by COVID-19 and SARS-CoV-2 infection status (maternal participants)	In each subset of participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19, GMTs/GMCs and GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding IgG levels will be summarized using the same statistical analysis method described for the secondary immunogenicity endpoints (maternal).
Immunogenicity from baseline to before Dose 2 (Phase 2 maternal participants)	In maternal participants enrolled in the Phase 2 portion of the study, GMTs/GMCs and GMFRs of SARS-CoV-2 neutralizing titers and full-length S-binding IgG levels at baseline and before Dose 2 will be summarized using the same statistical analysis method described for the secondary immunogenicity endpoints (maternal).
Immunogenicity (infant participants by breastfeeding status)	For infants breastfed and not breastfed, respectively, GMCs at birth and 6 months after delivery, and GMFRs for full-length S-binding IgG levels, will be summarized using the same statistical analysis method described for the secondary immunogenicity endpoints for maternal participants.
Safety (infant participants by breastfeeding status)	For infants breastfed and not breastfed, respectively, counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with AEs from birth through 1 month of age, and SAEs and AESIs through 6 months of age, will be provided by vaccine group according to the study intervention the maternal participants received.
COVID-19 incidence rate (infant participants)	Counts, incidence of COVID-19 per 1000 person-years of follow-up, and the associated 2-sided 95% CIs will be provided for each vaccine group in the infants participants.

Endpoint	Statistical Analysis Methods
MIS-C cases (infant participants)	Counts, incidence of MIS-C per 1000 person-years of follow-up, and the associated 2-sided 95% CIs will be provided for each vaccine group in the infants participants.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

9.5.1. Analysis Timing

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

- Safety data through 1 month after delivery for the first approximately 600 randomized maternal participants.
- Immunogenicity data through 1 month after Dose 2 from the immunogenicity subset for immunobridging assessment of SARS-CoV-2 neutralizing titers to nonpregnant female participants 18 to 55 years of age from the Phase 3 C4591001 study.
- Complete safety and immunogenicity analysis after complete data are available or at the end of the study.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses conducted while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

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

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. 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 to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

The participant must be informed that 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 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 her right to access and correct her personal data and to withdraw consent for the processing of her personal data.

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

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

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

Before any study-specific activity is performed, the investigator, or a person designated by the investigator, will obtain written informed consent from each maternal participant. This will include written informed consent for the mother and the fetus during the pregnancy, and the infant's continuation in the study after delivery. Informed consent will be obtained from the father of the fetus/infant if mandated by local requirements.

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

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

10.1.4. 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 her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents Within Marketing Authorization Packages/Submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.9. 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.

10.1.10. Sponsor's Qualified Medical Personnel

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

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

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

For maternal immunization clinical studies conducted in pregnant women, data on the EDP as well as pregnancy outcome are collected and analyzed in the clinical database. For these studies, in general, EDP cases are not reportable unless associated with SAEs/nonserious AEs.

The term "participant" in this section refers to (1) the maternal participant and her fetus; and after delivery (2) the maternal participant and (3) the infant participant.

10.2.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

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

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

10.2.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) 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 via occupational exposure	Occupational exposure is not recorded.	Occupational exposure (regardless of whether associated with an AE) Note: Include all AEs/SAEs associated with occupational exposure.

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

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE 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 completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

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

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

10.3. Appendix 3: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug Induced Liver Injury

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

LFTs are not required as a routine safety monitoring procedure 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.

Studies that include more detailed hepatic safety assessments (eg, an external hepatic expert panel or DMC that has separate definitions and charter) will still need to follow the reporting guidelines described below for applicable cases.

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 Hepatic Injury Council (HIC) should be informed if such a situation occurs during the study; the HIC will provide the necessary support to the study team.

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. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered.

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

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

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

10.4. Appendix 4: 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/mm3 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.

10.5. Appendix 5: 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
app	application
BiPaP	bilevel positive airway pressure
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransferase
AV	atrioventricular
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CVA	cerebrovascular accident
DART	developmental and reproductive toxicology
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
EDD	estimated delivery date
e-diary	electronic diary

Abbreviation	Term
EDP	exposure during pregnancy
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GA	gestational age
GBS	group B streptococcus
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
HBV	hepatitis B virus
HCP	healthcare provider
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIC	Hepatic Injury Council
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G
IL-6	interleukin 6
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IWR	interactive Web-based response
LDH	lactate dehydrogenase

Abbreviation	Term
LFT	liver function test
LLOQ	lower limit of quantitation
LMP	last menstrual period
LNP	lipid nanoparticle
LS	least squares
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
NaCl	sodium chloride
NI	noninferiority
NIMP	noninvestigational medicinal product
PASS	postauthorization safety study
P2 S	SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein
PaO_2	partial pressure of oxygen, arterial
PD	pharmacodynamic(s)
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TBili	total bilirubin
T_H1	T-helper type 1
ULN	upper limit of normal
US	United States
VE	vaccine efficacy
WHO	World Health Organization

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Document Approval Record

Document Name:	C4591015 Protocol Amendment 2 Clean Copy, 02 Mar 2021
Document Title:	A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEALTHY PREGNANT WOMEN 18 YEARS OF AGE AND OLDER

Signed By:	Date(GMT)	Signing Capacity
Lockhart, Stephen Paul	02-Mar-2021 14:00:27	Business Line Approver
Koury, Kenneth	02-Mar-2021 15:02:21	Final Approval
De Bernardi, Barbara	02-Mar-2021 22:33:25	EUQPPV Approval