Protocol C4591015

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

Statistical Analysis Plan (SAP)

Version: 3

Date: 31 Mar 2022

[redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
1/ 24 Mar 2021	Protocol Amendment 2, 02 Mar 2021	N/A
2/ 07 Jun 2021	Protocol Amendment 3, 14 May 2021	1. Implemented the changes made in protocol amendment 3. 2. Deleted all content in Section 5.1.2 and the hypothesis test part in Section 6.2.1.1.1. 3. Added "chills" to the definition of confirmed COVID-19 in maternal participants in Appendix 2.
3/ 31 Mar 2022	Protocol Amendment 5, 08 Mar 2022	1. Implemented the changes made in protocol amendment 5. 2. Deleted content in Section 5 and revised to clarify that no hypothesis test will be done because of sample size reduction. 3. Removed model-based GMR and sensitivity analysis in Section 6.1.2. 4. Changed the selection of nonpregnant participants from Study C4591001 to 1:1 age matching to maternal participants in Section 3.1.2.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591015. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 2 below.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules (Section 5.3). No other missing information (eg, missing e-diary data) will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (see Section 4 for definition). 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 (see Section 4 for definition). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by the all-available efficacy (mITT) populations. Missing laboratory results will not be imputed.

Table 2. List of Primary, Secondary, and Exploratory 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 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 describe the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation and reference 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 female participants complying with the key protocol criteria (evaluable 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 describe the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation and reference 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 female 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 women 1 month after Dose 2	• SARS-CoV-2 neutralizing titers

Table 2. List of Primary, Secondary, and Exploratory Objectives, Estimands, and Endpoints

Objectives[a]	Estimands	Endpoints
Secondary	**Secondary**	**Secondary**
To describe 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
To describe 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
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 to 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

Table 2. List of Primary, Secondary, and Exploratory Objectives, Estimands, and Endpoints

Objectives[a]	Estimands	Endpoints
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): • 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

Table 2. List of Primary, Secondary, and Exploratory Objectives, Estimands, and Endpoints

Objectives[a]	Estimands	Endpoints
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
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.

2.2. Study 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 350 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 200 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.

The Phase 3 portion of this study will include approximately 150 pregnant women at a 1:1 randomization ratio to assess the safety, tolerability, and immunogenicity of BNT162b2 among pregnant women enrolled at 24 to 34 weeks' gestation. Phase 3 will proceed after the first 200 maternal participants have been enrolled in Phase 2.

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

Enrollment in this study was terminated on 25 Oct 2021 with approximately 350 participants enrolled. Enrollment was terminated because of enrollment challenges into a placebo-controlled study as a result of universal recommendations for COVID-19 vaccination of pregnant women and the increased global availability of COVID-19 vaccines. Enrollment numbers within this protocol have been modified accordingly.

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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Endpoints (Maternal Participants)

- Prompted local reactions (redness, swelling, and pain at the injection site) for up to 7 days following each dose in each vaccine group
- Prompted systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following each dose in each vaccine group
- AEs from Dose 1 through 1 month after Dose 2
- SAEs from Dose 1 through 1 month after delivery

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. Maternal participants originally randomized to placebo who subsequently receive BNT162b2 1 month following delivery will not complete a reactogenicity e-diary after receiving BNT162b2.

This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 3 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of each dose.

Table 3. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable	Yes (1)	No (0)
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	For each local reaction, participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).

Note: Missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 4.

Table 4. Local Reaction Grading Scale

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

For each local reaction reported for each dose, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each dose) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 4), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. However, if a reaction is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing reaction would be the date/day that the next vaccine is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day after vaccination that a reaction is reported of any severity.

For the onset day of each local reaction, if participants report a change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, vomiting, diarrhea, headache, fatigue/tiredness, chills, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

Oral temperature will be collected in the evening, daily, for 7 days following each dose (Days 1 through 7, where Day 1 is the day of each dose) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 6 below.

Table 6. Scale for Fever

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

Note: Fever is defined as temperature ≥38.0°C (≥100.4°F).

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7)
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7)
- Duration (first to last day reported) of use of antipyretic medication
- Onset day of use of antipyretic medication

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.4. Adverse Events

For maternal participants, AEs will be assessed from the time of informed consent through 1 month after Dose 2. Additionally, for those maternal participants who originally received placebo and subsequently receive BNT162b2, AEs will be collected from the first dose through 1 month after the second dose of BNT162b2. AEs will be categorized according to MedDRA terms.

The primary safety endpoint "AEs from Dose 1 through 1 month after Dose 2" and other AE endpoints will be summarized by SOC and PT at the participant level.

This primary safety endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose). AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent to 6 months after delivery for maternal participants originally randomized to BNT162b2 or through 1 month after the second dose of BNT162b2 for maternal participants who originally received placebo and subsequently receive BNT162b2. SAEs will be categorized according to MedDRA terms.

The primary safety endpoint "SAEs from Dose 1 through 1 month after delivery" will be summarized by SOC and PT at the participant level.

3.1.2. Immunogenicity Endpoints (Maternal Participants)

- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in maternal participants and nonpregnant women without serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection

- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in maternal participants and nonpregnant women with or without past SARS-CoV-2 infection

The maternal participants randomized to BNT162b2 group in this study and a group of nonpregnant female participants selected from the Phase 3 C4591001 trial who received BNT162b2 will be included in the primary analysis. The nonpregnant participants will be selected based on 1:1 age matching to the maternal participants.

Values below the LLOQ will be set to 0.5 × LLOQ for the analysis. The LLOQ value for neutralizing titers will be included in the analysis specification once it is available.

3.2. Secondary Endpoints

3.2.1. Vaccine Efficacy Endpoints

- COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT in maternal participants without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection

- COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT in maternal participants with or without evidence of past SARS-CoV-2 infection

- Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion in maternal participants without serological or virological evidence of prior SARS-CoV-2 infection

3.2.2. Immunogenicity Endpoints (Maternal Participants)

- Full-length S-binding IgG levels at baseline, 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery and fold rises in full-length S-binding IgG levels from baseline to each subsequent time point

- SARS-CoV-2 neutralizing titers at baseline, 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery and fold rises in SARS-CoV-2 neutralizing titers from baseline to each subsequent time point

Values below the LLOQ will be set to 0.5 × LLOQ for the analysis. The LLOQ value for full-length S-binding IgG will be included in the analysis specification once it is available.

3.2.3. Safety Endpoints (Infant Participants)

- Specific birth outcomes
- AEs from birth through 1 month of age
- SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age

3.2.4. Immunogenicity Endpoint (Infant Participants)

- Full-length S-binding IgG levels at birth and 6 months after delivery and fold rise in full-length S-binding IgG levels from birth to 6 months after delivery

3.3. Exploratory Endpoints

3.3.1. COVID-19 Incidence Rate (Maternal Participants)

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT from 7 days after the second dose of BNT162b2 in participants who received BNT162b2 at initial randomization

3.3.2. Asymptomatic SARS-CoV-2 Infection (Maternal Participants)

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in maternal participants who received BNT162b2 at initial randomization and without evidence of prior SARS-CoV-2 infection

3.3.3. Serological Responses by COVID-19 and SARS-CoV-2 Infection Status (Maternal Participants)

- Full-length S-binding IgG levels at baseline, 1 month after Dose 2, at delivery, and 6 months after delivery and fold rises in full-length S-binding IgG levels from baseline to each subsequent time point
- SARS-CoV-2 neutralizing titers at baseline, 1 month after Dose 2, at delivery, and 6 months after delivery and fold rises in SARS-CoV-2 neutralizing titers from baseline to each subsequent time point

These endpoints will be summarized by COVID-19 and SARS-CoV-2 infection status:

- Confirmed COVID-19
- Confirmed severe COVID-19
- SARS-CoV-2 infection but no confirmed COVID-19

3.3.4. Immune Response Between Dose 1 and Dose 2 (Phase 2 Maternal Participants)

- Full-length S-binding IgG levels at baseline and before Dose 2 and fold rise in full-length S-binding IgG levels from baseline to before Dose 2
- SARS-CoV-2 neutralizing titers at baseline and before Dose 2 and fold rise in SARS-CoV-2 neutralizing titers from baseline to before Dose 2

The pre–Dose 2 blood samples for immunogenicity will be drawn from maternal participants in Phase 2 only.

3.3.5. Immune Response by Breastfeeding Status (Infant Participants)

- Full-length S-binding IgG levels at birth and 6 months after delivery and fold rise in full-length S-binding IgG levels from birth to 6 months after delivery by breastfeeding status

3.3.6. Safety Endpoints by Breastfeeding Status (Infant Participants)

- AEs from birth through 1 month of age by breastfeeding status
- SAEs and AESIs (major congenital anomalies, developmental delay) through 6 months of age by breastfeeding status

3.3.7. COVID-19 Incidence Rate (Infant Participants)

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

3.3.8. MIS-C Cases (Infant Participants)

- MIS-C incidence per 1000 person-years of follow-up

3.4. Other Endpoints

All safety, immunogenicity, and efficacy endpoints described above will be summarized separately for participants with confirmed stable HIV infection.

3.5. Baseline and Other Variables

For maternal participants, measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments. For infant participants, measurements or samples collected at birth are considered the starting time points for the assessments.

3.5.1. Demographics, Medical History, and Physical Examination

For both maternal and infant participants, the demographic variables are date of birth, sex (male or female, for infant participants only), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported). In cases where more than 1 category is selected for race, the category “multiracial” will be created and used for analysis.

The maternal participants also have the demographic variable age at Dose 1 (in years), which is derived based on the maternal participant's birthday. For example, if the vaccination day is 1 day before the maternal participant's 19th birthday, the maternal participant is considered to be 18 years old. For maternal participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at Dose 1 for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation. The infant participants also have the demographic variable gestational age at birth (in weeks).

Medical history for maternal participants will be categorized according to MedDRA. Comorbidities that increase the risk for severe COVID-19 illness will be categorized based on medical history terms.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the maternal participant at Visit 1 and the infant participant at birth, a physical examination will be performed and any findings recorded in the source documents and, if clinically significant, it will be recorded on the medical history CRF for maternal participants and on the AE CRF for infant participants.

3.5.2. E-Diary Transmission

For maternal participants, an e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. E-diary data will not be collected from maternal participants originally assigned to placebo who subsequently receive BNT162b2 after delivery.

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- 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 will be recorded in the CRF.
- Prohibited medications listed in the protocol, 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.

The following concomitant medications will be recorded in the CRF for infant participants:

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

Prior and concomitant vaccines and concomitant medications will be coded using the WHO Drug Dictionary.

3.6. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the primary safety endpoints. Specific birth outcomes and AESIs (major congenital anomalies, developmental delay) have been described above in the secondary safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety, immunogenicity, and efficacy results in the table below. For the specified criteria in each population definition that are not associated with unblinded information (randomized vaccine or vaccine actually received), data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and the classifications will be documented per standard operating procedures.

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 participants who 1. are eligible and randomized; 2. receive 2 doses of the vaccine to which they are randomized, with Dose 2 received within the predefined window (19-42 days, inclusive, after Dose 1); 3. have at least 1 valid immunogenicity result within an appropriate window 1 month after Dose 2 (28-42 days, inclusive, after Dose 2); and 4. have no other important protocol deviations as determined by the clinician.
Dose 1 evaluable immunogenicity (maternal)	All participants who 1. are eligible and randomized; 2. receive Dose 1 of the vaccine to which they are randomized; 3. have at least 1 valid immunogenicity result within an appropriate window 1 month after Dose 1 (19-23 days, inclusive); and 4. have no other important protocol deviations as determined by the clinician.
Evaluable immunogenicity (infant)	All infant participants born to evaluable immunogenicity maternal participants and have no important protocol deviations as determined by the clinician.
All-available immunogenicity (maternal)	All randomized 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, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
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.

Population	Description
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.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity/efficacy, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the corresponding all-available immunogenicity population if there is over 10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which the maternal participants were randomized.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

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

The 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 throughout the study. Further details can be found in the protocol, Section 6.3. The timing for statistical analyses is specified in Section 7.

5.1. Hypotheses and Decision Rules

Due to early enrollment termination and reduced sample size, all endpoints will be analyzed descriptively without formal hypothesis tests.

5.2. General Methods

Unless specified otherwise, "vaccine group" in this document is based on the study intervention (BNT162b2 or placebo) to which the maternal participants are randomized or that they receive. The vaccine group of the infant participants will follow the vaccine group of their mothers. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless otherwise specified.

Missing reactogenicity e-diary data will not be imputed; missing start AE dates will be handled according to the Pfizer safety rules.

5.2.1. Analyses for Binary Data

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

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen[2] method.

The 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. No Tier 1 events have been identified to date for BNT162b2.

- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 1% participants with the AE term in at least 1 vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

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

AEs and SAEs reported for maternal participants during the open-label follow-up period will be summarized separately.

5.2.2. Analyses for Continuous Data

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

5.2.2.1. Geometric Means

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

5.2.2.2. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results at the designated time point to the results at baseline (defined as before vaccination for maternal participants and at birth for infant participants). 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.

5.2.2.3. Geometric Mean Ratios

GMR is defined as the ratio of the GM of antibody titers/concentrations in the 2 comparison groups.

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.

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant, following the Pfizer standard of handling incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

The LLOQ for each assay will be provided by Vaccine Research and Development as part of the electronic data transfer or within the Clinical Testing Completion Memo prior to statistical analysis. Assay results above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety Endpoints (Maternal Participants)

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of maternal participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (maternal) (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each and any local reaction after each dose in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Confirmed e-diary errors will be excluded from the analysis. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplementary Analyses

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population as above, and appropriate analysis methodology and reporting results. Confirmed e-diary errors will be excluded from these analyses.

- Duration (days) of each local reaction after each dose.
- Onset day of each local reaction after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

In addition, the proportions of participants reporting each prompted local reaction after any dose will be summarized by maximum severity level.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of maternal participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (maternal) (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplementary Analyses

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after each dose.
- Onset day of each systemic event after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

In addition, the proportions of participants reporting each prompted systemic event after any dose will be summarized by maximum severity level.

Figures:

Bar charts with the proportions of participants for each systemic event throughout 7 days after each dose will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of maternal participants reporting AEs from Dose 1 through 1 month after Dose 2 (Section 2.1).
- Analysis set: Safety population (maternal) (Section 4).
- Analysis time point: Dose 1 through 1 month after Dose 2.
- Analysis methodology: Descriptive statistics and 3-tiered approach (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs from Dose 1 through 1 month after Dose 2 will be provided for each vaccine group. For both Tier 1 (if any) and Tier 2 events, the between-group difference in proportions and the associated 95% CI based on the Miettinen and Nurminen[2] method will be provided. For Tier 1 events (if any), the asymptotic p-values for the difference in proportions will be provided. For Tier 3 events, counts and percentages will be provided for each vaccine group.

6.1.1.3.2. Supplementary Analyses

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group. Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group if the number of immediate AEs is sufficiently large; otherwise, they will be listed only.

All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of maternal participants reporting SAEs from Dose 1 through 1 month after delivery (Section 2.1).
- Analysis set: Safety population (maternal) (Section 4).
- Analysis time point: Dose 1 through 1 month after delivery.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial SAE start dates (Section 5.3).
- Reporting results: 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.

6.1.2. Immunogenicity Endpoints (Maternal Participants)

6.1.2.1. SARS-CoV-2 Neutralizing Titers at 1 Month After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection

6.1.2.1.1. Main Analyses

- Estimand: GMR of the SARS-CoV-2 neutralizing titers in pregnant women to those in nonpregnant women from Phase 3 of the C4591001 trial for participants without evidence of prior SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable immunogenicity population (maternal), all-available immunogenicity population (maternal) (as applicable) (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: GMR and associated 95% CI will be calculated as described in Section 5.2.2.3.
- Intercurrent events and missing data: Titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: GMRs and associated 2-sided 95% CIs will be provided.

6.1.2.2. SARS-CoV-2 Neutralizing Titers in Participants With and Without Evidence of Prior SARS-CoV-2 Infection

6.1.2.2.1. Main Analyses

- Estimand: GMR of SARS-CoV-2 neutralizing titers in pregnant women to those in nonpregnant women from Phase 3 of the C4591001 trial for participants with and without evidence of prior SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable immunogenicity population (maternal), all-available immunogenicity population (maternal) (as applicable) (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: GMR and associated 95% CI will be calculated the same way as for the participants without evidence of infection (Section 5.2.2.3).
- Intercurrent events and missing data: Titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: GMRs and associated 2-sided 95% CIs will be provided.

6.2. Secondary Endpoints

6.2.1. Vaccine Efficacy Endpoints

6.2.1.1. COVID-19 Incidence per 1000 Person-Years of Blinded Follow-Up Based on Central Laboratory or Locally Confirmed NAAT

6.2.1.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [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 without evidence of prior SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 through 1 month after delivery per 1000 person-years of blinded follow-up in maternal participants with and without evidence of prior SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy population (maternal), all-available efficacy population (maternal) (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).

- Analysis methodology: Assessment of VE will be performed for confirmed COVID-19 illness (using the first definition in Appendix 2) from 7 days after Dose 2 through 1 month after delivery, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of 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 (see Appendix 2 for details on the derivation of IRR and VE).

- Intercurrent events and missing data: Missing data (symptom is present without laboratory testing data) will not be imputed.

- Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.2.1.1.2. Supplemental Analyses

The same assessment of VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be performed for confirmed COVID-19 illness based on CDC-defined symptoms (using the second definition in Appendix 2).

All COVID-19 cases after Dose 1 may be analyzed using the Dose 1 all-available efficacy population. Kaplan-Meier cumulative incidence curves may be provided.

6.2.1.2. Incidence of Asymptomatic Infection of SARS-CoV-2 Based on N-Binding Antibody Seroconversion

6.2.1.2.1. Main Analyses

- Estimand:

  - 100 × (1 – IRR) [ratio of incidence of asymptomatic infection of SARS-CoV-2 through 1 month after delivery in evaluable maternal participants without evidence of prior SARS-CoV-2 infection for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy population (maternal), all-available efficacy population (maternal) (Section 4).

- Analysis time point: End of the surveillance period.

- Analysis methodology: Assessment of VE will be performed for the incidence of asymptomatic infection of SARS-CoV-2 through 1 month after delivery, and will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of incidence of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group through 1 month after delivery (see Appendix 2 for details on the definition of asymptomatic infection and the derivation of IRR and VE).

- Intercurrent events and missing data: Missing N-binding data will not be imputed.

- Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.2.2. Immunogenicity Endpoints (Maternal Participants)

6.2.2.1. Full-Length S-Binding IgG Levels and SARS-CoV-2 Neutralizing Titers

6.2.2.1.1. Main Analyses

- Estimands:
  - GMCs of full-length S-binding IgG levels (Section 2.1).
  - GMTs of SARS-CoV-2 neutralizing titers (Section 2.1).
  - GMFRs from before vaccination to each subsequent time point after vaccination for full-length S-binding IgG levels and SARS-CoV-2 neutralizing titers (Section 2.1).
- Analysis set: Evaluable immunogenicity population (maternal), all-available immunogenicity population (maternal) (as applicable) (Section 4).
- Analysis time points: Baseline, 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery.
- Analysis methodology: GMs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Concentrations/titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: GMCs/GMTs and 2-sided 95% CIs will be provided for each vaccine group before vaccination and at each subsequent time point after vaccination. GMFRs and 2-sided 95% CIs will be provided for each vaccine group from before vaccination to each subsequent time point after vaccination.

Figures:

Empirical RCDCs will be provided for full-length S-binding IgG levels and SARS-CoV-2 neutralizing titers at each time point for each vaccine group (Section 5.2.2.4).

6.2.3. Safety Endpoints (Infant Participants)

6.2.3.1. Specific Birth Outcomes

6.2.3.1.1. Main Analyses

- Estimand: The percentage of infant participants reporting specific birth outcomes (Section 2.1).

- Analysis set: Safety population (infant) (Section 4).
- Analysis time point: Birth.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with specific birth outcomes will be provided for each vaccine group (according to the study intervention the maternal participants received).

6.2.3.2. Adverse Events

6.2.3.2.1. Main Analyses

- Estimand: The percentage of infant participants reporting AEs from birth through 1 month of age (Section 2.1).
- Analysis set: Safety population (infant) (Section 4).
- Analysis time point: Birth through 1 month of age.
- Analysis methodology: Descriptive statistics and 3-tiered approach (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with AEs from birth through 1 month of age will be provided for each vaccine group (according to the study intervention the maternal participants received). For both Tier 1 (if any) and Tier 2 events, the between-group difference in proportions and the associated 95% CI based on the Miettinen and Nurminen[2] method will be provided. For Tier 1 events (if any), the asymptotic p-values for the difference in proportions will be provided. For Tier 3 events, counts and percentages will be provided for each vaccine group (according to the study intervention the maternal participants received).

6.2.3.3. Serious Adverse Events and AESIs

6.2.3.3.1. Main Analyses

- Estimand: The percentage of infant participants reporting SAEs and AESIs (major congenital anomalies, developmental delay) from birth through 6 months of age (Section 2.1).
- Analysis set: Safety population (infant) (Section 4).
- Analysis time point: Birth through 6 months of age.

- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial SAE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with SAEs and AESIs from birth through 6 months of age will be provided for each vaccine group (according to the study intervention the maternal participants received).

6.2.4. Immunogenicity Endpoint (Infant Participants)

6.2.4.1. Full-Length S-Binding IgG Levels

6.2.4.1.1. Main Analyses

- Estimands:
  - GMCs of full-length S-binding IgG levels (Section 2.1).
  - GMFR from birth to 6 months of age (Section 2.1).
- Analysis set: Evaluable immunogenicity population (infant), all-available immunogenicity population (infant) (as applicable) (Section 4).
- Analysis time points: Birth and 6 months of age.
- Analysis methodology: GMCs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFR will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: GMCs and 2-sided 95% CIs will be provided for each vaccine group (according to the study intervention the maternal participants randomized) at birth and 6 months of age. GMFRs and 2-sided 95% CIs will be provided for each vaccine group (according to the study intervention the maternal participants randomized) from birth to 6 months of age.

Figures:

Empirical RCDCs will be provided for full-length S-binding IgG levels at each time point for each vaccine group (Section 5.2.2.4).

6.3. Exploratory Endpoints

6.3.1. COVID-19 Incidence Rate (Maternal Participants)

6.3.1.1. COVID-19 Incidence per 1000 Person-Years of Follow-Up Based on Central Laboratory or Locally Confirmed NAAT

6.3.1.1.1. Main Analyses

- Estimands:
    - COVID-19 incidence based on central laboratory or locally confirmed NAAT from 7 days after the second dose of BNT162b2 per 1000 person-years of follow-up in maternal participants who received BNT162b2 at initial randomization (Section 2.1).
- Analysis set: Evaluable efficacy population (maternal), all-available efficacy population (maternal) (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness (using the first definition in Appendix 2) from 7 days after the second dose of BNT162b2 for participants who received BNT162b2 at initial randomization.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Incidence rates and the associated 2-sided 95% CIs will be provided.

6.3.1.1.2. Supplemental Analyses

The same analyses will be performed for confirmed COVID-19 illness based on CDC-defined symptoms (using the second definition in Appendix 2).

6.3.2. Asymptomatic SARS-CoV-2 Infection (Maternal Participants)

6.3.2.1. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-Up Based on N-Binding Antibody Seroconversion

6.3.2.1.1. Main Analyses

- Estimand:
    - Incidence of asymptomatic SARS-CoV-2 infection based on the N-binding antibody seroconversion through 6 months after delivery per 1000 person-years of follow-up in maternal participants who received BNT162b2 at initial randomization and without evidence of prior SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable efficacy population (maternal), all-available efficacy population (maternal) (Section 4).

- Analysis time point: End of the surveillance period.

- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for asymptomatic SARS-CoV-2 infection based on the N-binding antibody seroconversion (see Appendix 2 for the definition) through 6 months after delivery for participants who received BNT162b2 at initial randomization and without evidence of prior SARS-CoV-2 infection.

- Intercurrent events and missing data: Missing data will not be imputed.

- Reporting results: Incidence rate and the associated 2-sided 95% CI will be provided.

6.3.3. Serological Response by COVID-19 and SARS-CoV-2 Infection Status (Maternal Participants)

6.3.3.1. Full-Length S-Binding IgG Levels and SARS-CoV-2 Neutralizing Titers

6.3.3.1.1. Main Analyses

- Estimands:

  - GMCs of full-length S-binding IgG levels (Section 2.1)

  - GMTs of SARS-CoV-2 neutralizing titers (Section 2.1).

  - GMFR from before vaccination to each subsequent time point after vaccination for full-length S-binding IgG levels and SARS-CoV-2 neutralizing titers (Section 2.1).

- Analysis set: Evaluable immunogenicity population (maternal), all-available immunogenicity population (maternal) (as applicable) (Section 4) in each subset of maternal participants with confirmed COVID-19 (using the first definition in Appendix 2), confirmed severe COVID-19 (using the first definition in Appendix 2), and SARS-CoV-2 infection without confirmed COVID-19 (using the first definition in Appendix 2).

- Analysis time points: Baseline, 1 month after Dose 2, at delivery, and 6 months after delivery.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs will be calculated as described in Section 5.2.2.2.

- Intercurrent events and missing data: Concentrations/titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.

- Reporting results: GMCs/GMTs and 2-sided 95% CIs will be provided for each vaccine group before vaccination and at each subsequent time point after vaccination. GMFRs and 2-sided 95% CIs will be provided for each vaccine group from before vaccination to each subsequent time point after vaccination.

6.3.3.1.2. Supplemental Analyses

The same analyses will be performed in each subset of maternal participants with confirmed COVID-19 (using the second definition in Appendix 2), confirmed severe COVID-19 (using the second definition in Appendix 2), and SARS-CoV-2 infection without confirmed COVID-19 (using the second definition in Appendix 2).

6.3.4. Immune Response After Dose 1 (Phase 2 Maternal Participants)

6.3.4.1. Full-Length S-Binding IgG Levels and SARS-CoV-2 Neutralizing Titers

6.3.4.1.1. Main Analyses

- Estimands:
  - GMCs of full-length S-binding IgG levels (Section 2.1).
  - GMTs of SARS-CoV-2 neutralizing titers (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination for full-length S-binding IgG levels and SARS-CoV-2 neutralizing titers (Section 2.1).
- Analysis set: Dose 1 evaluable immunogenicity population (maternal), Dose 1 all-available immunogenicity population (maternal) (as applicable) (Section 4) in maternal participants enrolled in the Phase 2 portion of the study.
- Analysis time points: Baseline and before Dose 2.
- Analysis methodology: GMs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Concentrations/titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: GMCs/GMTs and 2-sided 95% CIs will be provided for each vaccine group before vaccination and at each subsequent time point after vaccination. GMFRs and 2-sided 95% CIs will be provided for each vaccine group from before vaccination to each subsequent time point after vaccination.

Figures:

Empirical RCDCs will be provided for full-length S-binding IgG levels and SARS-CoV-2 neutralizing titers at baseline and before Dose 2 for each vaccine group (Section 5.2.2.4).

6.3.5. Immune Response by Breastfeeding Status (Infant Participants)

6.3.5.1. Full-Length S-Binding IgG Levels

6.3.5.1.1. Main Analyses

- Estimands:
  - GMCs of full-length S-binding IgG levels (Section 2.1).
  - GMFRs from birth to 6 months of age (Section 2.1).
- Analysis set: Evaluable immunogenicity population (infant), all-available immunogenicity population (infant) (as applicable) (Section 4) by breastfeeding status.
- Analysis time points: Birth and 6 months of age.
- Analysis methodology: GMCs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Concentrations/titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: GMCs and 2-sided 95% CIs will be provided for each vaccine group (according to the study intervention the maternal participants randomized) at birth and 6 months of age. GMFRs and 2-sided 95% CIs will be provided for each vaccine group (according to the study intervention the maternal participants randomized) from birth to 6 months of age.

6.3.6. Safety Endpoints by Breastfeeding Status (Infant Participants)

6.3.6.1. Adverse Events

6.3.6.1.1. Main Analyses

- Estimand: The percentage of infant participants reporting AEs from birth through 1 month of age (Section 2.1).
- Analysis set: Safety population (infant) (Section 4) by breastfeeding status.
- Analysis time point: Birth through 1 month of age.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).

- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with AEs from birth through 1 month of age will be provided for each vaccine group (according to the study intervention the maternal participants received).

6.3.6.2. Serious Adverse Events and AESIs

6.3.6.2.1. Main Analyses

- Estimand: The percentage of infant participants reporting SAEs and AESIs (major congenital anomalies, developmental delay) from birth through 6 months of age (Section 2.1).
- Analysis set: Safety population (infant) (Section 4) by breastfeeding status.
- Analysis time point: Birth through 6 months of age.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial SAE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs for infant participants with SAEs and AESIs from birth through 6 months of age will be provided for each vaccine group (according to the study intervention the maternal participants received).

6.3.7. COVID-19 Incidence Rate (Infant Participants)

6.3.7.1. COVID-19 Incidence per 1000 Person-Years of Follow-Up Based on Central Laboratory or Locally Confirmed NAAT

6.3.7.1.1. Main Analyses

- Estimand:
  - COVID-19 incidence based on central laboratory or locally confirmed NAAT per 1000 person-years of follow-up in infants born to maternal participants from each vaccine group (Section 2.1).
- Analysis set: All-available efficacy population (infant) (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness (using the first definition in Appendix 2) for infants born to maternal participants from each vaccine group.
- Intercurrent events and missing data: Missing data will not be imputed.

- Reporting results: 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 (according to the study intervention the maternal participants randomized).

6.3.7.1.2. Supplemental Analyses

The same analyses will be performed for confirmed COVID-19 illness (using the second definition in Appendix 2).

6.3.8. MIS-C Cases (Infant Participants)

6.3.8.1. MIS-C Incidence per 1000 Person-Years of Follow-Up

6.3.8.1.1. Main Analyses

- Estimand:
  - MIS-C incidence per 1000 person-years of follow-up in infants born to maternal participants from each vaccine group (Section 2.1).
- Analysis set: All-available efficacy population (infant) (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed MIS-C cases (see Appendix 2 for the definition) for infants born to maternal participants from each vaccine group.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: 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 (according to the study intervention the maternal participants randomized).

6.4. Other Endpoints

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

For maternal participants, 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.

6.5. Subset Analysis

Subgroup analyses based on race and ethnicity will be performed on all primary safety and immunogenicity endpoints (as supplemental analyses).

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

6.6.1.1. Demographic Characteristics

For maternal participants, demographic characteristics, including age at Dose 1, race, ethnicity, and classification of BMI, will be summarized for the safety population (maternal) for each vaccine group and overall.

For infant participants, demographic characteristics, including sex, race, ethnicity, and gestational age at birth, will be summarized for the safety population (infant) for each vaccine group and overall.

6.6.1.2. Medical History

For maternal participants, each reported medical history term will be mapped to a SOC and PT according to MedDRA. The number and percentage of vaccinated maternal participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group for the safety population (maternal).

The number and proportion of maternal participants with comorbidities that increase the risk for severe COVID-19 illness will be summarized by each vaccine group.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

The number and percentage of randomized maternal participants and their infant participants will be included in the maternal and infant participant disposition summary, respectively.

For maternal participants, the numbers and percentages of participants who received vaccinations (Doses 1 and 2 for both vaccine groups, Doses 3 and 4 for the original placebo group), who completed the follow-up visits (1 month after Dose 2, at delivery, 1 month after delivery, 6 months after delivery for the original active group, 1 month after Dose 4 for the original placebo group), and who withdrew before each follow-up visit, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

For infant participants, the number of participants who completed the study (6 months after birth) and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to the study intervention the maternal participants randomized). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately, along with the reasons for exclusion, by vaccine group.

6.6.2.2. Blood Samples for Assay

The number and percentage of randomized maternal participants and their infant participants providing blood samples within and outside of protocol-specified time frames will be tabulated separately for each time point.

6.6.2.3. Transmission of E-Diaries

The numbers and percentages of vaccinated maternal participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period will be summarized by as-received vaccine group for each dose.

The safety population (maternal) will be used.

6.6.3. Study Vaccination Exposure

6.6.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of maternal participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for all randomized maternal participants. The denominator for the percentages is the total number of randomized maternal participants in the given vaccine group or overall.

In addition, the relation of randomized vaccine to vaccine actually received will be presented as a cross tabulation of the vaccine actually received versus the randomized vaccine.

A listing of maternal participants showing the randomized vaccine and the vaccine actually received at each dose will be presented.

6.6.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification.

For maternal participants, all vaccines received within 14 days before Dose 1 will be listed. The number and percentage of maternal participants receiving each concomitant vaccine after Dose 1 will be tabulated by vaccine group. The safety population (maternal) will be used. Concomitant medications for maternal participants will be summarized in a similar way as concomitant vaccines.

For infant participants, all concomitant medications received from birth will be listed. The number and percentage of infant participants receiving each concomitant medication after birth will be tabulated by vaccine group. The safety population (infant) will be used.

6.7. Safety Summaries and Analyses

Local reaction, systemic event, AE, and SAE summaries and analyses are described under Primary Safety Endpoints (Section 6.1.1).

7. 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.

7.1. Analysis Timing

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

- Immunogenicity data through 1 month after Dose 2 from all randomized maternal participants for assessment of SARS-CoV-2 neutralizing titers.
- Complete safety, immunogenicity, and efficacy analysis after complete data are available or at the end of the study.

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.

7.2. Data Monitoring Committee

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

8. REFERENCES

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3. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8. DOI: 10.1097/01.PCC.0000149131.72248.E6.

4. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19–associated multisystem inflammatory syndrome in children—United States, March–July 2020. MMWR Morb Mortal Wkly Rep. 2020;69(32):1074-80.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
ATC	Anatomic Therapeutic Chemical
BiPaP	bilevel positive airway pressure
BLQ	below the limit of quantitation
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRF	case report form
CRP	C-reactive protein
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
ESR	erythrocyte sedimentation rate
FiO_2	fraction of inspired oxygen
GI	gastrointestinal
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HR	heart rate
ICD	informed consent document
ICU	intensive care unit
IgG	immunoglobulin G
IL-6	interleukin 6
IRC	internal review committee
IRR	illness rate ratio
IWR	interactive Web-based response
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children

Abbreviation	Term
mITT	modified intent-to-treat
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
PaO_2	partial pressure of oxygen, arterial
PT	preferred term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SpO_2	oxygen saturation as measured by pulse oximetry
ULN	upper limit of normal
VE	vaccine efficacy
WHO	World Health Organization

Appendix 2. IRR and VE Derivation

COVID-19 Case Definition

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

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

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

Confirmed Severe COVID-19, first definition: 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.

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 the principal investigator, it is deemed necessary:

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

Confirmed Severe Infant COVID-19 definition: 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[3];
- 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[4]:
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.

Surveillance Times

Fundamental to VE assessment is the surveillance, for each participant, for cases satisfying various endpoints that may occur during the trial. Endpoint and participant combinations where surveillance is applicable require identification of the start and the end of the surveillance period in order to determine the participant-level endpoint surveillance time. For all COVID-19 VE-related endpoints in this study, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy (maternal)	Dose 2 + 7 days
Dose 2 all-available efficacy (maternal)	Dose 2 + 7 days
Dose 1 all-available efficacy (mITT) (maternal)	Dose 1

For all COVID-19 VE-related endpoints in this study, the end of a surveillance period for each participant is the earliest of the following events:

- When the first COVID-19 case occurs.
- When the participant's end of the study occurs (eg, because of withdrawal, death, or trial completion).
- When the participant has his or her first important protocol violation.
- When the participant is unblinded at 1 month after delivery.

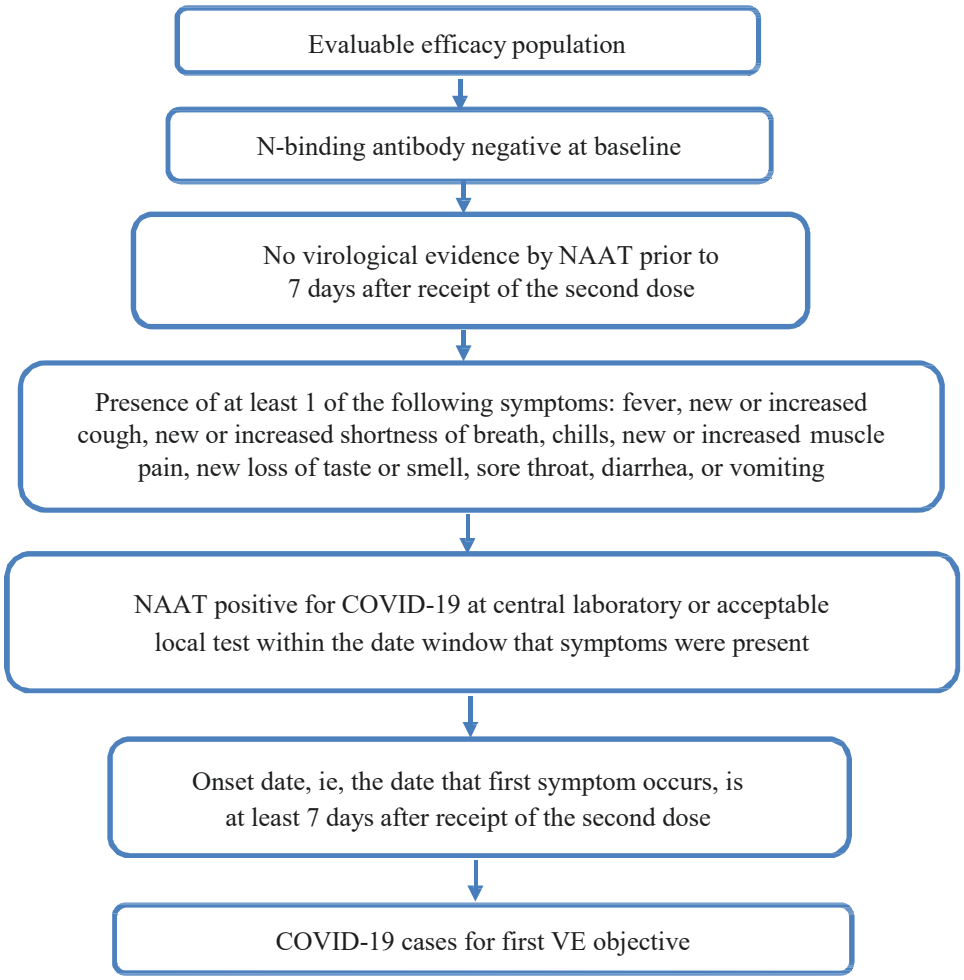
For descriptive assessment of exploratory endpoints of COVID-19 incidence rate (maternal and infant), the surveillance period is defined the same way except that unblinding at 1 month after delivery will not be considered as the end of the surveillance period.

Specific information regarding VE-related endpoint surveillance start and end times by endpoint will be provided in Analysis and Reporting Plan specification documents.

Once the COVID-19 cases and surveillance period have been identified, VE can be calculated as 100 × (1 – IRR), where IRR is the ratio of confirmed COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group.

Flowcharts

1. The flowchart for deriving the COVID-19 cases included below for the first VE endpoint in evaluable efficacy participants with no serological or virological evidence of past SARS-CoV-2 infection:



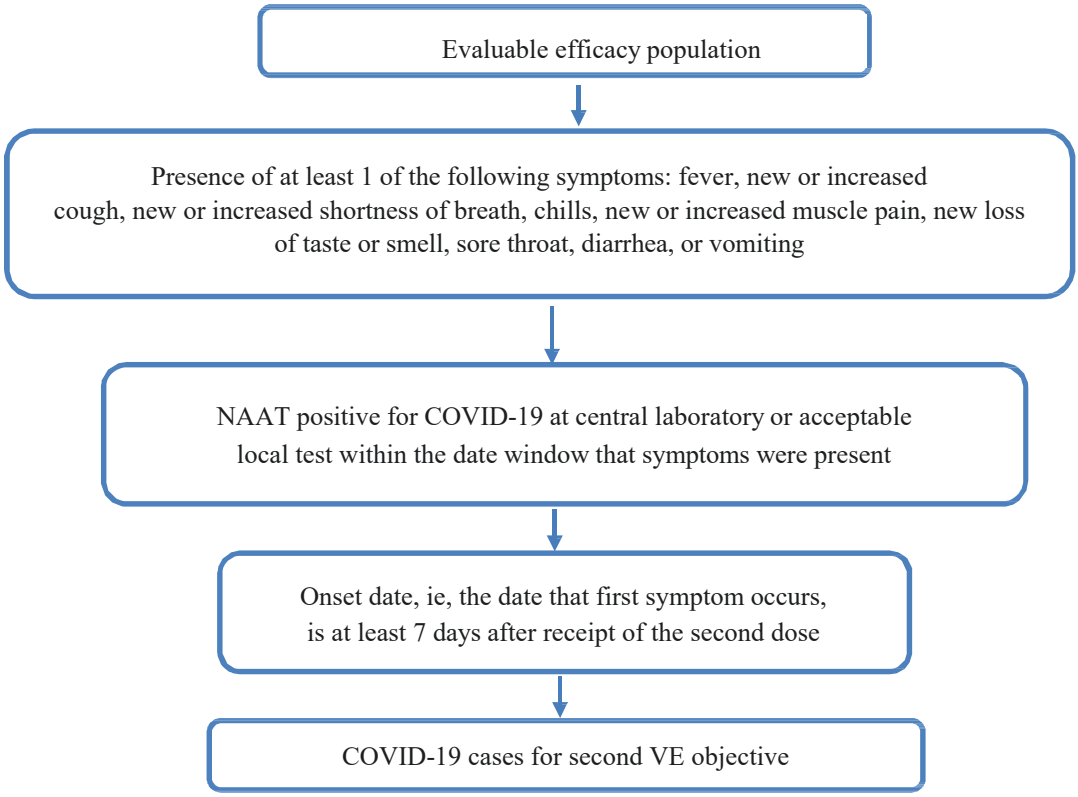
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

b. Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)

c. Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

2. The flowchart for deriving the COVID-19 cases included below for the second VE endpoint in evaluable efficacy participants:



Asymptomatic Case Definition

An asymptomatic case is defined as positive N-binding antibody at a post–Dose 2 visit (eg, Visit 4, 1 month after Dose 2) in participants without serological or virological evidence of infection prior to that visit, determined by negative N-binding antibody at Visit 1 and negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness. A secondary definition will be applied without the requirement for a negative NAAT at Visit 2.

Surveillance Times

For the asymptomatic cases based on N-binding antibody seroconversion, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	**Start-of-Surveillance Time**
Evaluable efficacy (maternal)	Dose 2
Dose 2 all-available efficacy (maternal)	Dose 2
Dose 1 all-available efficacy (mITT) (maternal)	Dose 1

The end of a surveillance period for each participant is the earliest of the following:

- Date of the first positive N-binding antibody result after Dose 2.
- Date of the participant's last post–Dose 2 N-binding antibody test that is prior to a COVID-19 symptom associated with a nonnegative NAAT result.
- Date of the participant's last post–Dose 2 N-binding antibody test that is prior to an important protocol violation (for analysis based on the evaluable efficacy population).

Once the asymptomatic cases and surveillance periods have been identified, VE can be calculated as 100 × (1 – IRR), where IRR is the ratio of incidence of asymptomatic infection per 1000 person-years of follow-up for the active vaccine group to the placebo group.