Protocol C3671003

A PHASE 2b, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE IN PREGNANT WOMEN 18 THROUGH 49 YEARS OF AGE AND THEIR INFANTS

Statistical Analysis Plan (SAP)

Version: 2 (Amendment 1)

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 13 Aug 2019	Amendment 1/ 18 Jun 2019	N/A	N/A
2 (Amendment 1)/ 18 Nov 2019	Amendment 1/ 18 Jun 2019	• Updated description of evaluable maternal population as not all maternal subjects will have a 1 month postvaccination visit. • Removed a planned analysis and a subset analysis • Added details for clarity	• Updated the author's job title • Updated the evaluable maternal population (in Section 4) to remove reference to "1 month after vaccination" for the blood draw and to specify time frame of assay results. • Updated the evaluable infant population (in Section 4) to make it more time point–specific • Updated Section 6.4 (Table 8 and Table 9) to remove the reference to subset analysis for GA subgroup "27 to <33 weeks" • Updated Section 7.2 with new information regarding available assay data and added text regarding "preliminary evaluable populations" • Updated Section 7.2 to remove reference to a planned analysis on 500 US participants

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671003. A brief description of the study design and the study objectives is given below. Subsequent sections describe analysis populations and give the definitions of the safety and immunogenicity endpoints followed by details of statistical reporting. A list of tables, listings and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. 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.

As the first study of Pfizer's respiratory syncytial virus (RSV) vaccine in the maternal immunization setting, data from this study will be critical for business decisions regarding the future development of the vaccine in maternal immunization. Specifically, this study will determine whether the safety and immunogenicity profile of the vaccine is sufficiently promising for Pfizer to proceed to studies of efficacy. Also, if that is the case, this study will provide the data to select the dose and formulation of the vaccine to be used in future studies. Criteria to be used in making those development decisions are beyond the scope of this SAP.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Primary Objectives

2.1.1.1. Primary Objective: Maternal Participants

- To describe the safety and tolerability of an RSV vaccine in women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.

2.1.1.2. Primary Objective: Infant Participants

- To assess the safety of maternal immunization in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.

2.1.2. Secondary Objectives

2.1.2.1. Secondary Objective: Maternal Participants

- To describe the immune responses elicited by an RSV vaccine in women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.

2.1.2.2. Secondary Objective: Infant Participants

- To describe RSV antibody levels in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.

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2.1.4. Primary Estimands

2.1.4.1. Primary Estimands: Maternal Participants

- **Percentage of maternal participants reporting local reactions.**

This estimand includes the following 4 attributes:

  - Population: Maternal participants who receive 1 dose of investigational product.
  - Variable: Presence/absence of prespecified local reactions within 7 days after vaccination.
  - Intercurrent event(s): For participants who discontinue, all collected data will be included; missing data will not be imputed.
  - Population-level summary: Percentage of maternal participants reporting local reactions in each vaccine group.

- **Percentage of maternal participants reporting systemic events.**

This estimand includes the following 4 attributes:

  - Population: Maternal participants who receive 1 dose of investigational product.
  - Variable: Presence/absence of prespecified systemic events within 7 days after vaccination.
  - Intercurrent event(s): For participants who discontinue, all collected data will be included; missing data will not be imputed.
  - Population-level summary: Percentage of maternal participants reporting systemic events in each vaccine group.

- **Percentage of maternal participants reporting adverse events (AEs) from the time of vaccination through 1 month after vaccination.**

This estimand includes the following 4 attributes:

  - Population: Maternal participants who receive 1 dose of investigational product.
  - Variable: Presence of AEs within 1 month after vaccination.
  - Intercurrent event(s): For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
  - Population-level summary: Percentage of maternal participants reporting AEs through 1 month after vaccination in each vaccine group.

- **The percentage of maternal participants reporting obstetric complications, medically attended adverse events (MAEs), and serious adverse events (SAEs) throughout the study.**

This estimand includes the following 4 attributes:

- Population: Maternal participants who receive 1 dose of investigational product.
- Variable: Presence/absence of the event of interest throughout the study.
- Intercurrent event(s): For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Population-level summary: Percentage of maternal participants reporting obstetric complications, MAEs, and SAEs throughout the study in each vaccine group.

2.1.4.2. Primary Estimands: Infant Participants

- **Percentage of infant participants with specific birth outcomes.**

This estimand includes the following 4 attributes:

- Population: Infant participants born to the maternal participants receiving 1 dose of investigational product.
- Variable: Presence/absence of specific birth outcomes.
- Intercurrent event(s): No intercurrent events to be taken into account.
- Population-level summary: Percentage of infant participants with specific birth outcomes in each vaccine group.

- **Percentage of infant participants having AEs.**

This estimand includes the following 4 attributes:

- Population: Infant participants born to the maternal participants receiving 1 dose of investigational product.
- Variable: Presence/absence of AEs from birth to 1 month, CCI [redacted]
- Intercurrent event(s): For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Population-level summary: Percentage of infant participants with AEs CCI [redacted] from birth to 1 month in each vaccine group.

- **Percentage of infant participants having SAEs, AEs of special interest, and MAEs through 12 months of age.**

This estimand includes the following 4 attributes:

  - Population: Infant participants born to the maternal participants receiving 1 dose of investigational product.

  - Variable: Presence/absence of SAEs, AEs of special interest, and MAEs. These will be collected through 12 months of age, except for those congenital anomalies that occur during intrauterine life and can be identified prenatally, at birth, or later in life.

  - Intercurrent event(s): For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

  - Population-level summary: Percentage of infant participants with the event of interest during the first 12 months of life in each vaccine group.

2.1.5. Secondary Estimands

2.1.5.1. Secondary Estimands: Maternal Participants

- **Immune response estimated by the geometric mean titer (GMT) for RSV A− and RSV B−neutralizing antibody titers.**

This estimand estimates the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. It includes the following 4 attributes:

  - Population: Maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants).

  - Variable: Antibody titer results before vaccination, 2 weeks and 1 month after vaccination, and at delivery.

  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed.

  - Population-level summary: GMT for RSV A− and RSV B−neutralizing antibody titers.

- **Immune response estimated by the geometric mean fold rise (GMFR) from baseline in RSV A– and RSV B–neutralizing antibody titers.**

This estimand estimates the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. It includes the following 4 attributes:

  - Population: Maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants).

  - Variable: Fold rise from before vaccination to 2 weeks and 1 month after vaccination and at delivery in antibody titers.

  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.

  - Population-level summary: GMFR from baseline for RSV A– and RSV B–neutralizing antibody titers.

- **Geometric mean ratio (GMR) estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group to the placebo group.**

This estimand estimates the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. It includes the following 4 attributes:

  - Population: Maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants).

  - Variable: Antibody titers before vaccination, 2 weeks and 1 month after vaccination, and at delivery.

  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.

  - Population-level summary: GMR estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group to the placebo group.

2.1.5.2. Secondary Estimands: Infant Participants

- **Functional antibody levels estimated by the GMT for RSV A– and RSV B–neutralizing antibody titers.**

This estimand estimates the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. It includes the following 4 attributes:

  - Population: Infants born to maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants).
  - Variable: Antibody titers at birth and at 1, 2, 4, and 6 months of age.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.
  - Population-level summary: GMT for RSV A– and RSV B–neutralizing antibody titers.

- **GMR estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group to the placebo group.**

This estimand estimates the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. It includes the following 4 attributes:

  - Population: Infants born to maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants).
  - Variable: Antibody titers at birth and at 1, 2, 4, and 6 months of age.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.
  - Population-level summary: GMR estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group to the placebo group.

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2.2. Study Design

This is a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study in which approximately 650 healthy pregnant women ≥18 through ≤49 years of age will be randomized to receive one of 2 dose levels of bivalent (RSV subgroup A and subgroup B) RSV vaccine candidate at 120 µg (60 µg A and 60 µg B) and 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, formulated with or without aluminum hydroxide ($Al[OH]_3$), or placebo (1:1:1:1:1 randomization). Assessments will include descriptions of safety, tolerability, and immunogenicity in maternal participants as well as safety and characteristics of transplacentally transferred antibodies in their infants. CCI [redacted] accination of mothers will occur at a time of year such that the infant is likely to be exposed to RSV during the first 6 months of life.

This study will use stopping rules. An internal review committee (IRC) and an external data monitoring committee (E-DMC) will monitor safety in this study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Endpoints: Maternal Participants

- Prespecified local reactions within 7 days after vaccination.
- Prespecified systemic events within 7 days after vaccination.
- AEs from the time of vaccination through 1 month after vaccination.
- Obstetric complications, MAEs, and SAEs throughout the study.

3.1.2. Primary Endpoints: Infant Participants

- Specific birth outcomes.
- AEs from birth to 1 month of age CCI [redacted].
- SAEs, AEs of special interest (major congenital anomalies, developmental delay), and MAEs through 12 months of age. Major congenital anomalies (defined as structural or functional anomalies [eg, metabolic disorders] that occur during intrauterine life and can be identified prenatally, at birth, or later in life).

3.2. Secondary Endpoints

3.2.1. Secondary Endpoint: Maternal Participants

- RSV A– and RSV B–neutralizing antibody titers measured before vaccination, at 2 weeks and 1 month after vaccination, and at delivery.

3.2.2. Secondary Endpoint: Infant Participants

- RSV A– and RSV B–neutralizing antibody titers measured at birth and at 1 month, 2 months, 4 months, and 6 months of age depending on the assigned blood sampling schedule.

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3.4. Baseline Variables

3.4.1. Baseline Variables: Maternal Participants

Day 1 is defined as the day of vaccination and the start of the reporting period for local reactions and systemic events in the electronic diary (e-diary) for maternal participants.

Laboratory data will be collected for maternal participants only. Data are collected during the screening visit, Visit 0 (-14 to -2 days prior to vaccination), and will be considered baseline data.

Day 1 is considered the baseline visit for the following assessments: immunogenicity, obstetric examination, and vital signs.

3.4.2. Baseline Variables: Infant Participants

Day 1 is defined as the day of birth (Visit 1) for the infant participants.

Day 1 is considered the baseline visit for the following assessments: immunogenicity (cord blood sample collected at birth), physical examination, and vital signs.

3.5. Safety Endpoints

3.5.1. Adverse Events

AEs will be captured and reported in accordance with Pfizer reporting standards.

For maternal participants the time period for actively eliciting and collecting AEs and SAEs ("active collection period") begins from the time the maternal participant provides informed consent, which is obtained before participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 1 month (30 days) after the last administration of the investigational product. In this study, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through 1 month after vaccination. From 1 month after vaccination until the maternal participant completes the study, MAEs and SAEs will be collected.

For infant participants, the time period for actively eliciting and collecting AEs and SAEs ("active collection period") begins at birth and continues through and including a minimum

of 28 days after birth. From Visit 2 until the last study visit, only AEs of special interest, MAEs, and SAEs, including hospitalizations, will be reported.

For maternal participants who are screen failures, the active collection period ends when screen failure status is determined. If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

During the active collection period, both nonserious AEs and SAEs are recorded on the case report form (CRF) and will be categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product for maternal participants.

An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. From Visit 2 (for infant participants) or from 1 month after vaccination (for maternal participants) until the participant completes the study, MAEs and SAEs will be collected.

AEs of special interest for infant participants are major congenital anomalies and developmental delays and are collected from birth through the end of the study (12-month-of-age visit).

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In addition, AEs occurring up to 48 hours after blood draws or collection of nasal swabs that are related to study procedures must be reported in the CRF.

A 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 (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier 2 events: These are events that are not Tier 1 but are "common." A MedDRA preferred term (PT) is defined as a Tier 2 event if there are 4 or more participants in any vaccine group reporting the event within 30 days.

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

3.5.2. Reactogenicity Data

Reactogenicity data are prompted AEs collected using an e-diary, during Days 1 through 7, starting on the day of vaccination (Day 1). The reactogenicity data will include local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain).

3.5.2.1. Local Reactions

Local reactions reported in the e-diary are redness, swelling, and pain at the injection site.

Presence of Local Reactions (Proportion of Participants Reporting)

The participant will record the presence or absence of pain at the injection site in the e-diary as "Mild," "Moderate," "Severe," or "None." Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. A participant with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

Only an investigator is able to classify a maternal participant's local reaction as Grade 4, after clinical evaluation of the maternal participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. If a maternal participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected on the unscheduled reactogenicity page and as an AE on the CRF. The AE event will be graded using the AE intensity grading scale as indicated in the table "Assessment of Intensity" in Section 10.3.3 of the protocol.

The presence or absence of each local reaction on a given day is defined as follows:

= "Missing," if the value is missing on a given day;

= "Yes," if the participant reports the reaction as "Yes" for redness or swelling (with a diameter of 2.5 cm or more) **or** "Mild," "Moderate," "Severe," or "Grade 4" for pain at the injection site on a given day;

= "No," if the participant reports the reaction as "No" for redness or swelling **or** "None" for pain at the injection site on a given day.

For each local reaction, the derivation of whether or not the specific reaction occurred on "any day (Day 1-7)" will be made. The derivation of this variable is given in Table 2 below.

Table 2. Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Participant reports the reaction as "Yes" on any day from Day 1 through Day 7.	Participant reports the reaction as "No" on all 7 days or as a combination of "No" and missing on all 7 days.	Participant reports the reaction as missing on all 7 days.

a. The variable will be defined for each of the 3 local reactions.

For "any local reaction" on any day, a similar definition can be applied as given in Table 3 below.

Table 3. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Participant reports any redness or swelling >2.0 cm or "Yes" for pain at injection site on any day during Days 1 through 7.	Participant reports redness or swelling ≤2.0 cm or pain at injection site as "No" on all 7 days or as a combination of above and missing on all 7 days for all 3 local reactions.	Participant reports all of the local reactions as missing on all 7 days.

Grading Scale for Local Reactions

The grading of local reactions is listed below in Table 4.

Table 4. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
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 (>20 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 (>20 measuring device units)	Necrosis
Pain (at the injection site)	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Only an investigator is able to classify a maternal participant's local reaction as Grade 4, after clinical evaluation of the maternal participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the maternal participant. Grade 4 assessment should be made by the investigator using the AE severity grading scale. The assessment will be collected on the AE case report form.

Maximum Severity for Local Reactions

The maximum severity (highest grading) of each local reaction within 7 days after vaccination will be derived. The maximum severity will be derived as follows:

= "Missing," if values are missing for all days from Day 1 through Day 7;

= 0, if the participant reports all reactions as "No" or a combination of missing and "No" for all days from Day 1 through Day 7;

= *highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "No" for at least 1 day.

Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction + 1). 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 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.

Onset of Local Reaction

The onset day of each local reaction and any local reaction will be derived.

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

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

In summary, the following variables will be derived for local reaction:

1. Presence or absence of each local reaction on each day (Days 1-7) after vaccination.
2. Presence or absence of each local reaction on "any day (Day 1-7)" after vaccination.
3. Presence or absence of any local reaction on "any day (Day 1-7)" after vaccination.
4. Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.
5. Duration of each local reaction after vaccination.
6. Onset day of each local reaction after vaccination.
7. Onset day of any local reaction after vaccination.

3.5.2.2. Systemic Events

Systemic events reported via the e-diary are fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain. The participant is to document the presence or absence of systemic events in the e-diary as "Mild," "Moderate," "Severe," or "None." Participants are to be asked to assess the severity of each event according to Table 5 below.

Only an investigator is able to classify a maternal participant's systemic event as Grade 4, after physical evaluation of the maternal participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. If a maternal participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. A Grade 4 event will be collected on the unscheduled reactogenicity page and as an AE on the CRF. The event will be graded using the AE

severity grading scale (see Section 10.3.3 of the protocol). Further, for all ongoing systemic events on Day 7, the stop date will be recorded in the CRF.

Table 5. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe nausea
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
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

a. Only an investigator is able to classify a maternal participant's systemic event as Grade 4, after clinical evaluation of the maternal participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the maternal participant. Grade 4 assessment should be made by the investigator using the AE severity grading scale. The assessment will be collected on the AE case report form.

The highest temperature for each day for 7 days after vaccination is to be recorded in the e-diary. The protocol defines fever as an oral temperature ≥100.4°F (≥38.0°C). For ongoing fever on Day 7, the stop date will be recorded in the CRF. Any temperatures recorded as <35.0°C or >42.0°C will be treated as data-entry errors and excluded from the analyses. For reporting purposes, fever will be analyzed using the following temperature grading scale as displayed in Table 6.

Table 6. Grading Scale for Fever

Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
≥38.0°C to 38.4°C	>38.4°C to 38.9°C	>38.9°C to 40.0°C	>40.0°C

The presence or absence of each systemic event on a given day is defined as follows:

= "Missing," if the value is missing on a given day;

= "Yes," if the participant reports a temperature ≥38.0°C for fever **or** "Mild," "Moderate," "Severe," or "Grade 4" for the remaining events on a given day;

= "No," if the participant reports a temperature <38.0°C for fever **or** "None" for the remaining events on a given day.

For each systemic event, the following variables will be derived:

1. Presence or absence of each systemic event on each day (Days 1-7) after vaccination.
2. Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
3. Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.
4. Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
5. Duration of each systemic event after vaccination.
6. Onset day of each systemic event after vaccination.
7. Onset day of any systemic event after vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.5.2.1). "Any systemic event" includes any fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain.

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3.5.4. Laboratory Data

Blood samples for hematology and blood chemistry assessments (approximately 10 mL) will be collected for all maternal participants at screening.

Assessments will include:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, white blood cell (WBC) count, total neutrophils (absolute [Abs]), eosinophils (Abs), monocytes (Abs), basophils (Abs), and lymphocytes (Abs).

- Blood chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.

The toxicity grading scale in Table 7 below for pregnant women will be adapted, as appropriate (eg, based on the pregnancy status at the visit), for grading laboratory test abnormalities.

Table 7. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Female hemoglobin (Hb), g/dL	Second trimester	9.7-14.8	9.0-9.6	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or life-threatening acute blood loss
	Change from baseline		1.6-2.0	2.1-4.5	4.6-5.0	>5.0
	Third trimester	9.5–15.0	9.0-9.4	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or life-threatening acute blood loss
	Change from baseline		1.6-2.0	2.1-4.5	4.6-5.0	>5.0
Platelets high, 1000 cells/mm^3	Second trimester	155-409	410-499	500-749	750-1000	>1000
	Third trimester	146-429	430-499	500-749	750-1000	>1000
Platelets low, 1000 cells/mm^3	Second trimester	155-409	125-154	100-124	25-99	<25
	Third trimester	146-429	125-146	100-124	25-99	<25
WBCs[a] high, 1000 cells/mm^3	Second trimester	5.6-14.8	>14.8-16.0	>16.0-20.0	>20.0-25.0	>25.0 signs of septic shock
	Third trimester	5.9-16.9	>16.9-18.0	>18.0-20.0	>20.0-25.0	>25.0 signs of septic shock
WBCs[a] low, 1000 cell/mm^3	Second trimester	5.6-14.8	<5.5-3.5	<3.5-1.4	<1.4-1.0	<1.0 signs of septic shock
	Third trimester	5.9-16.9	<5.9-3.5	<3.5-1.4	<1.4-1.0	<1.0 signs of septic shock
Neutrophils (absolute neutrophil count), 1000 cells/mm^3	Second trimester	3.8-12.3	<3.8-2.0	<2.0-1.0	<1.0-0.5	<0.5
	Third trimester	3.9-13.1	<3.9-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils (absolute), 1000 cells/mm^3	Second trimester	0-0.6	>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic
	Third trimester	0-0.6	>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic
Monocytes (absolute), 1000 cells/mm^3	Second trimester	0.1-1.1	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
	Third trimester	0.1-1.4	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
Basophils (absolute), 1000 cells/mm^3	Second trimester	0-0.1	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
	Third trimester	0-0.1	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
Lymphocytes high (absolute), 1000 cells/mm^3	Second trimester	0.9-3.9	>3.9-5.0	>5.0		
	Third trimester	1.0-3.6	>3.6-5.0	>5.0		

Table 7. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Lymphocytes low (absolute) 1000 cells/mm^3	Second trimester	0.9-3.9	<0.9-0.75	<0.75-0.5	<0.5-0.25	<0.25
	Third trimester	1.0-3.6	<1.0-0.75	<0.75-0.5	<0.5-0.25	<0.25
Blood urea nitrogen (BUN), mg/dL	Second trimester	3-13	14-19	20-30	>30	Requires dialysis
	Third trimester	3-11	12-19	20-30	>30	Requires dialysis
Creatinine, mg/dL	Second trimester	0.4-0.8	0.9-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
	Third trimester	0.4-0.9	1-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
Aspartate aminotransferase (AST[b]), U/L	Second trimester	3-33	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c] cirrhosis transplant candidate
	Third trimester	4-32	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c] cirrhosis transplant candidate
Alanine aminotransferase (ALT[d]), U/L	Second trimester	2-33	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>10 x ULN[c]
	Third trimester	2-25	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c] cirrhosis transplant candidate
Total bilirubin (with increased LFTs[e]), mg/dL	Second trimester	0.1-0.8	>1.0-1.2 x ULN[c]	>1.2-1.5 x ULN[c]	>1.5-1.8 x ULN[c]	>1.8 x ULN[c]
	Third trimester	0.1-1.1	>1.0-1.2 x ULN[c]	>1.2-1.5 x ULN[c]	>1.5-1.8 x ULN[c]	>1.8 x ULN[c]
Total bilirubin (with normal LFTs[e]), mg/dL	Second trimester	0.1-0.8	>1.0-1.5 x ULN[c]	>1.5-2.0 x ULN[c]	>2.0-3.0 x ULN[c]	>3.0 x ULN[c]
	Third trimester	0.1-1.1	>1.0-1.5 x ULN[c]	>1.6-2.0 x ULN[c]	>2.0-3.0 x ULN[c]	>3.0 x ULN[c]
Alkaline phosphatase, U/L	Second trimester	25-126	1.1-2.0 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c]
	Third trimester	38-229	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c]

a. WBC = white blood cell.
b. AST = aspartate aminotransferase.
c. ULN = upper limit of normal.
d. ALT = alanine aminotransferase.
e. LFT = liver function test.

3.5.5. Physical Examination, Including Vital Signs

3.5.5.1. Physical Examination, Including Vital Signs: Maternal Participants

Physical examination will be performed at the screening visit (Visit 0) and will include any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Height and weight will also be measured and recorded.

Vital signs including sitting systolic and diastolic blood pressure, heart rate, and oral temperature will be measured at the screening visit (Visit 0), prior to vaccination on Day 1, at the 2-week follow-up, and at the 1-month follow-up and recorded in the CRF.

3.5.5.2. Physical Examination, Including Vital Signs: Infant Participants

The physical examination will be performed at all scheduled visits and will include any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; back; musculoskeletal; extremities; genitourinary; neurological; and lymph nodes.

Length, head circumference, and weight will also be measured and recorded.

Rectal temperature, heart rate, and respiratory rate will be assessed at all visits; additionally, oxygen saturation by pulse oximetry will be assessed at birth CCI [redacted] All attempts should be made to help ensure that measurements are taken while the infant is resting quietly.

3.5.6. Obstetric Examination

Obstetric examination findings will be collected at screening through the 1-month follow-up visit. The obstetric examination will include, but is not limited to, scars from previous deliveries, fundal height, fetal heart tones, and fetal movement.

The following information regarding pregnancy outcome will be collected: date of delivery, location of delivery (medical facility, home, other), mode of delivery (vaginal, cesarean section), cesarean type (elective, semielective, emergency), delivery complications (yes, no), number of births, outcome at delivery (full-term live birth, premature live birth, stillbirth, spontaneous abortion, induced/elective abortion), gross visual inspection of the aborted fetus/stillbirth (not done, no observed abnormalities, observed abnormalities), and pathology performed (yes, no).

3.5.7. Birth Outcome: Infant Participants

Infant outcome at birth will be collected at the delivery visit and includes the following: gestational age (weeks, days); Apgar (appearance, pulse, grimace, activity, and respiration) score at 1, 5, and 10 minutes; Ballard score; infant cry immediately after delivery (yes, no); infant suckle shortly after delivery (yes, no); newborn normal (yes, no); congenital malformation/anomaly (yes, no); and other neonatal problem/abnormality (yes, no). Infant vital status (live, stillbirth) will also be included. Neonatal death will be derived using the

response to "delivery outcome" from the pregnancy outcome and the AE data. Neonatal death is defined as the death of a live-born infant that occurred within a month after birth.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the informed consent document.
Randomly assigned to investigational product	All maternal participants who are assigned a randomization number in the interactive response technology (IRT) system.
Evaluable – Maternal	All maternal participants who: • are eligible; • receive the investigational product to which they were randomized; • have blood drawn for assay testing within the protocol-specified time frames ; • have at least 1 valid and determinate assay result after vaccination; and • have no major protocol violations. Participants will be analyzed according to the investigational product as randomized.
Evaluable – Infant	All infant participants who: • are eligible; • are born to the maternal participants who received the investigational product to which they were randomized and who have no major protocol violations before delivery; • have blood drawn for assay testing within the protocol-specified time frame at birth[a]; • have at least 1 valid and determinate assay result at birth[a]; and • have no major protocol violations. Participants will be analyzed according to the investigational product as randomized to their mothers.
Modified intent-to-treat (mITT) – Maternal	All randomized maternal participants who receive investigational product and have at least 1 valid and determinate assay result for the proposed analysis. Participants will be analyzed according to the investigational product as randomized.
mITT – Infant	All infant participants who are born to vaccinated maternal participants and have at least 1 valid and determinate assay result for the proposed analysis. Participants will be analyzed according to the investigational product as randomized to their mothers.
Safety – Maternal	All randomized maternal participants who receive investigational product. Participants will be analyzed according to the investigational product they actually received. A randomized participant who did not receive investigational product will be excluded from the safety analyses.

Population	Description
Safety – Infant	All infant participants who are born to vaccinated maternal participants. Participants will be analyzed according to the investigational product their mothers actually received. An infant born from a randomized maternal participant who did not receive investigational product will be excluded from the safety analyses.

a. Cord blood sample must be obtained on the day of birth. If cord blood is unavailable, a venous blood sample is to be collected up to 24 hours after birth.

Major protocol violations will be determined by clinical review (through the data handling memo). A major protocol violation is a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those participants with protocol violations before any immunogenicity analysis is carried out.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This Phase 2 study is designed to describe the safety, tolerability, and immunogenicity of RSV vaccine formulations in maternal participants and their infants. No formal statistical hypothesis testing will be performed. An estimation approach will be used to assess the safety and immunogenicity objectives.

Statistical decision rules will not be utilized in this study. All analyses are considered descriptive in nature.

5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the proportion (%) and the n (the numerator) and N (the denominator) used in the calculation of the proportion.

All analyses for both immunogenicity and safety data will be descriptive in nature.

All of the safety, tolerability, and immunogenicity data will be summarized by vaccine group of the maternal participants. Immunogenicity results will be analyzed separately for all the formulations. Within each participant group (maternal or infant), all participants who receive placebo will be combined as the control group. All data will be presented separately for maternal and infant participants. The only exception is the combined analysis of maternal-to-infant placental transfer ratio (infant/mother) of RSV A– and RSV B-neutralizing antibody titers.

Within maternal and infant groups, immunogenicity results may be summarized by formulation, dose level, and gestational age (GA).

5.2.1. Analyses for Binary Endpoints

The number and percentage of participants in each category will be summarized. The 95% CI for percentage, and for the difference in percentages, will also be presented, where appropriate.

The 95% CI for the proportion will be constructed by the Clopper-Pearson method described by Newcombe.[1] The 95% CI will be presented in terms of percentage.

The 95% CI for the difference in the proportions will be computed using the Chan and Zhang method.[2] The 95% CI will be presented in terms of percentage.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise specified, the CI for the mean of the continuous variables will be constructed by the standard method based on Student's t distribution.

5.2.2.1. Geometric Mean Titer (GMT)

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. GMT and associated 2-sided 95% CI will be calculated at each available time point for each vaccine group. 95% CI will be calculated by back transformation of the 95% CI for the mean of the logarithmically transformed assay results computed using Student's t distribution.

5.2.2.2. Geometric Mean Fold Rise (GMFR)

GMFR will be calculated as the mean difference of an individual participant's logarithmically transformed antibody levels (postvaccination minus prevaccination) and back transformed to the original units. 95% CI will be computed by back transformation of the 95% CI using 1-sample Student's t distribution for the mean difference of the logarithmically transformed assay results.

5.2.2.3. Geometric Mean Ratio (GMR)

The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units. Two (2)-sided 95% CI is also computed by back transformation of the CIs using 2-sample Student's t distribution for the mean difference of the logarithmically transformed assay results.

5.2.2.4. Reverse Cumulative Distribution Curves (RCDCs)

Reverse cumulative distribution curves (RCDCs) for RSV A– and RSV B–neutralizing antibody titers for a combination of available time points and vaccine groups will be generated.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in Pfizer's Vaccine Statistics Rulebook.

5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Day 1-7)" data will be considered nonmissing.

The reactogenicity data are collected through e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.5.2.

5.3.2. Immunogenicity Data

For GMT and GMC analysis, a titer reported as < lower limit of quantitation (LLOQ) will be converted to a value of ½ LLOQ. For calculating a fold rise, < LLOQ will be converted to ½ LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only one of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way. For any calculations, a titer reported as > upper limit of quantitation (ULOQ) will be converted to a value of ULOQ.

Values that are designated as serum quantity not sufficient (QNS), designated as indeterminate results, or recorded as "Not Done" will be set to missing. No imputation will be done for these missing values.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Endpoints: Maternal Participants

6.1.1.1. Local Reactions Within 7 Days After Vaccination

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
    - Presence or absence of each local reaction on each day (Days 1-7) after vaccination.

  - Presence or absence of each local reaction on "any day (Day 1-7)" after vaccination.
  - Presence or absence of any local reaction on "any day (Day 1-7)" after vaccination.
  - Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.
- For each group, n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables:
  - Duration of each local reaction after vaccination.
  - Onset day of each local reaction after vaccination.
  - Onset day of any local reaction after vaccination.

6.1.1.2. Systemic Events Within 7 Days After Vaccination

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of systemic event on each day (Days 1-7) after vaccination.
  - Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
  - Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.
- For each group, n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables:
  - Duration of each systemic event after vaccination.
  - Onset day of each systemic event after vaccination.
  - Onset day of any systemic event after vaccination.

6.1.1.3. AEs Within 1 Month After Vaccination

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics for Tier 3 events; difference and 95% CI between the vaccine group and the placebo group for Tier 2 events.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- For each group, number of participants with AEs within 1 month (30 days) (n), %, and 95% CI will be presented for any AE, each system organ class (SOC), and each PT within each SOC, by vaccine group. For AEs classified as Tier 2 events, difference in proportions and associated 2-sided 95% CI between the vaccine group and the placebo group will be presented.

6.1.1.4. Obstetric Complications, MAEs, and SAEs Throughout the Study

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- For each group, number of participants with obstetric complications, MAEs, and SAEs throughout the study (n), %, and 95% CI will be presented for any event, each SOC, and each PT within each SOC, by vaccine group.

6.1.2. Primary Endpoints: Infant Participants

6.1.2.1. Specific Birth Outcomes

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Analysis will be carried regardless of whether an intercurrent event occurs.
- For each group, number and proportion of participants with each birth outcome will be presented by vaccine group. In addition, difference in proportions and associated 2-sided 95% CI between the vaccine group and the placebo group will be presented.

6.1.2.2. AEs Within 1 Month of Age

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics for Tier 3 events; difference and 95% CI between the vaccine group and the placebo group for Tier 2 events.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- For each group, number of participants with AEs CCI [redacted] within 1 month (30 days) (n), %, and 95% CI will be presented for any AE, each SOC, and each PT within each SOC, by vaccine group. For AEs classified as Tier 2 events, difference in proportions and associated 2-sided 95% CI between the vaccine group and the placebo group will be presented.

6.1.2.3. AEs of Special Interest (Major Congenital Anomalies, Developmental Delays), MAEs, and SAEs Through 12 Months of Age

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- For each group, number of participants with AEs of special interest, MAEs, and SAEs through 12 months of age (n), %, and 95% CI will be presented for any event, each SOC, and each PT within each SOC, by vaccine group. For AEs of special interest, difference in proportions and associated 2-sided 95% CI between the vaccine group and the placebo group will be presented.

6.2. Secondary Endpoints

6.2.1. Secondary Endpoints: Maternal Participants

6.2.1.1. RSV A– and RSV B–Neutralizing Antibody Titers Measured Before Vaccination, at 2 Weeks and 1 Month After Vaccination, and at Delivery

6.2.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Evaluable (Section 4). Maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria.
- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- GMTs of the RSV A– and RSV B–neutralizing antibody titers at each available time point will be descriptively summarized for each vaccine group, along with associated 2-sided 95% CIs.

- GMFRs and associated 2-sided 95% CIs will be provided for RSV A– and RSV B-neutralizing antibody titers from before vaccination to each available time point after vaccination for each vaccine group.

- GMRs of the RSV vaccine group to the placebo group for the RSV A– and RSV B-neutralizing antibody titers at each available time point after vaccination will be calculated, along with associated 2-sided 95% CIs.

- RCDCs for RSV A– and RSV B–neutralizing antibody titers for a combination of prespecified time points and vaccine groups will be generated.

- Bar graphs of prevaccination and 1-month-postvaccination neutralizing GMTs will be produced for each vaccine group.

6.2.1.1.2. Supplementary Analysis

The main analysis will also be performed based on the mITT population if there is sufficient difference between the mITT population and the evaluable populations (an approximate 10% difference in the numbers of participants in each population).

The effects of formulation and dose on RSV A– and RSV B–neutralizing titers will be evaluated using an analysis of variance model with the log-transformed values of neutralizing titers at 1 month after vaccination. The model will include formulation and dose as main effects and their interaction. The F statistic and p-value for the main effects and interaction will be calculated. The least-square (LS) means, difference between the means, and 95% CI associated with these differences will be presented for each main effect. These will be exponentiated and presented in the original scale.

6.2.2. Secondary Endpoints: Infant Participants

6.2.2.1. RSV A– and RSV B–Neutralizing Antibody Titers Measured at Birth and at 1 Month, 2 Months, 4 Months, and 6 Months of Age Depending on the Assigned Blood Sampling Schedule

6.2.2.1.1. Main Analysis

- Estimand strategy: Hypothetical.

- Analysis set: Evaluable (Section 4). Infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria.

- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored. Results obtained from out-of-window blood draws will also be removed. Missing data will not be imputed.

- GMTs of the RSV A– and RSV B–neutralizing antibody titers at each available time point will be descriptively summarized for each vaccine group, along with associated 2-sided 95% CIs.

- GMRs of the RSV vaccine group to the placebo group for the RSV A– and RSV B-neutralizing antibody titers at each available time point after birth will be calculated, along with associated 2-sided 95% CIs.

- RCDCs for RSV A– and RSV B–neutralizing antibody titers for a combination of prespecified time points and vaccine groups will be generated.

6.2.2.1.2. Supplementary Analysis

The main analysis will also be performed based on the mITT population if there is enough difference between the mITT population and the evaluable population. This analysis will be performed only if there is enough difference (eg, ~10%) between the evaluable immunogenicity population and the mITT population.

In addition, GMTs of cord blood and GMTs of venous blood obtained within the first 24 hours after birth, along with associated 95% CIs, will be presented by maternal vaccine group. This analysis will be performed only if there is a sufficient number of cases in which venous blood was collected (eg, ~10%).

CCI

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[redacted]

6.4. Subset Analyses

Subgroup analyses of the secondary [redacted] immunogenicity endpoints will be performed, based on cohort (northern vs southern hemisphere), and subcategories of gestational age at the time of vaccination. Subgroup analyses for immunogenicity will be based on the respective evaluable immunogenicity population only. Table 8 and Table 9 summarize the defined subgroup analyses. Additional analyses (not defined here) may be performed if deemed necessary.

Table 8. Summary of Subgroup Analyses for Maternal Participants

Subgroup	Endpoints
Gestational age (GA) at the time of vaccination: 24 weeks ≤ GA <27 weeks 27 weeks ≤ GA <30 weeks 30 weeks ≤ GA <33 weeks GA ≥ 33 weeks	• RSV A– and RSV B–neutralizing antibody titers; [redacted] • Combined RSV A/B–neutralizing antibody titers; [redacted]
Cohort: Northern hemisphere Southern hemisphere	• RSV A– and RSV B–neutralizing antibody titers; [redacted] • Combined RSV A/B–neutralizing antibody titers; [redacted]

Table 9. Summary of Subgroup Analyses for Infant Participants

Subgroup	Endpoints
Maternal gestational age (GA) at the time of vaccination: 24 weeks ≤ GA <27 weeks 27 weeks ≤ GA <30 weeks 30 weeks ≤ GA <33 weeks GA ≥ 33 weeks	• RSV A– and RSV B–neutralizing antibody titers; [redacted] • Combined RSV A/B–neutralizing antibody titers; [redacted]

Table 9. Summary of Subgroup Analyses for Infant Participants

Subgroup	Endpoints
	C C
Cohort: Northern hemisphere Southern hemisphere	• RSV A– and RSV B–neutralizing antibody titers; •C C I • Combined RSV A/B–neutralizing antibody titers; C C I
Birth after vaccination: ≤14 days and >14 days	CCI
Birth after vaccination: ≤30 days and >30 days	CCI

CCI

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Baseline Summaries for Maternal Participants

For each vaccine group, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race and ethnicity), current substance use, and obstetric history as described in Section 3.5.6 will be generated for each vaccine group based on the safety population.

The number and proportion of participants with at least 1 medical history PT, arranged by SOC, will be tabulated for each vaccine group. The medical history summary is based on the safety population.

Participant data listings for demography and baseline characteristics data will also be generated.

6.5.1.2. Baseline Summaries for Infant Participants

Descriptive summary statistics for demographic characteristics will be generated by vaccine group based on the safety population.

Participant data listings for demography and other infant data will also be generated.

6.5.2. Study Conduct and Participant Disposition

The number and proportion of randomized participants will be included in the participant disposition summary. In addition, participants who completed the follow-up visit, and those who withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by vaccine group separately for maternal and infant participants. The reasons for withdrawal will be those as specified in the database.

Additionally, participants who missed at least 1 study procedure but continued in the study for safety follow-up will be summarized.

Participant disposition tables will be generated separately for maternal and infant participants.

Participants excluded from the evaluable immunogenicity and mITT populations will also be summarized with reasons for exclusion. These summaries will be generated separately for maternal and infant participants.

The numbers and proportions of participants who were randomized, were vaccinated, and had blood drawn within the protocol-specified time frame, and outside the specified window, will be tabulated by vaccine group. These summaries will be generated separately for maternal and infant participants.

The numbers and proportions of participants with e-diary data not transmitted, transmitted by day (Days 1-7), and transmitted on "all days" will be summarized by vaccine group. These summaries will be generated only for maternal participants.

Participant data listings of participants who withdrew during the study will be generated. Also, data listings for participants excluded from evaluable and mITT populations will be generated separately. These listings will be generated separately for maternal and infant participants.

The protocol deviations listings will be generated separately for maternal and infant participants. In addition, participants who did not receive the vaccine as randomized will be listed.

6.5.3. Concomitant Medications and Nondrug Treatments

Nondrug treatments, nonstudy vaccines, and medications taken after signing the informed consent will be categorized according to the World Health Organization (WHO) Drug Dictionary and summarized in accordance with the sponsor reporting standards. These will be generated separately for maternal and infant participants.

Antipyretic medication taken prior to vaccination by maternal participants may be summarized separately.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. C
CI
[redacted] There will be no adjustment for multiple comparison in the analyses.

Analyses and summaries of primary AE endpoints using the 3-tier approach are described in detail in Section 6.1.1 and Section 6.1.2.

Listings of participants reporting any AE and immediate AEs, and listings of all reported AEs will be generated. In addition, AEs occurring after participants signed the informed consent and prior to vaccination will also be listed.

All summaries and listings for the AEs will be generated separately for maternal and infant participants.

6.6.2. Reactogenicity Data

Analysis and summaries of primary reactogenicity endpoints are described in Section 6.1.1.1 and Section 6.1.1.2.

In addition, a participant data listing will be provided for all reactogenicity data as well as a listing for participants experiencing severe redness or swelling.

6.6.3. Laboratory Data

Descriptive summaries for laboratory abnormalities at screening will be provided by vaccine group. Also, separate listings for participants with abnormal laboratory results will be generated. These listings will be generated only for the maternal participants.

6.6.4. Physical Examination, Including Vital Signs

Descriptive summaries (counts and percentages) and listings based on the safety population will be provided in accordance with the Pfizer reporting standards. All summaries and listings for these data will be generated separately for maternal and infant participants.

6.6.5. Obstetric Examinations and Pregnancy Outcomes

Descriptive summaries and data listings will be generated for the obstetric examination findings and pregnancy outcomes. The summaries and listings for these data will be generated only for maternal participants.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis is planned for this study.

7.2. Interim Analyses and Summaries

The timing of the planned analyses prior to the final analysis is described below. For these analyses, depending on the availability of assay data, preliminary evaluable populations might be used.

1. An analysis will be performed when at least 250 maternal participants have given birth and cord blood RSV-neutralizing antibody titer data are available for the infants. Some available safety, tolerability, and immunogenicity data will be included in the analysis depending on the study needs. CCI [redacted]

2. An analysis will be performed when the delivery-visit RSV-neutralizing antibody titer data from all maternal and infant participants and the 1-month-after-birth visit data for all infant participants are available. All available safety, tolerability, and immunogenicity data will be included in the analysis. The analysis may include separate outputs for participants in the southern hemisphere.

3. An additional analysis will be performed when all data are available from the infant participants' 6-month visits. All available safety, tolerability, and immunogenicity data for both maternal and infant participants will be included in the analysis.

Additional analyses may be conducted at any time to support internal program-level decisions as needed. These analyses may be based on fewer than the total planned number of participants. Furthermore, these additional analyses may include tables and listings created specifically for the IRC and E-DMC. Refer to the IRC and E-DMC charters for further details.

The final analysis will be performed after all participants have completed the study and when all of the data are available.

8. REFERENCES

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17(8):857-72.

2. Chan ISF, Zhang Z. Test based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55(4):1202-9.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
e-diary	electronic diary
E-DMC	external data monitoring committee
GA	gestational age
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
C[redacted]	[redacted]
CI[redacted]	[redacted]
[redacted]	[redacted]
IRC	internal review committee
IRT	interactive response technology
LLOQ	lower limit of quantitation
CCI[redacted]	[redacted]
LS	least square
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
CCI[redacted]	[redacted]
PT	preferred term
QNS	quantity not sufficient
RBC	red blood cell
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSV vaccine	respiratory syncytial virus stabilized prefusion F subunit vaccine
CCI[redacted]	[redacted]
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SOC	system organ class
ULOQ	upper limit of quantitation
CCI	[redacted]
WBC	white blood cell
WHO	World Health Organization