Protocol C3671008

A PHASE 3, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN INFANTS BORN TO WOMEN VACCINATED DURING PREGNANCY

Statistical Analysis Plan
(SAP)

Version: 6

Date: 02 September 2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 28 May 2020	Protocol amendment 1 24 Mar 2020	Original version	N/A
2/ 21 January 2021	Protocol amendment 3 26 August 2020	• Updated different sections to match the protocol amendment 3. • Updated the healthcare utilization analysis per protocol amendment 3. • Updated the multiplicity adjustment method per CBER feedback.	• Updated the wording of 2 exploratory objectives (in Section 2.1.3.1) and endpoints (in Section 3.3.1) to match the amended protocol. • Updated the endpoint related to healthcare utilization (in Section 3.3.1) as well as Section 3.6 to match the amended protocol. • Updated the period for collecting MA-RTIs (in Section 3.5.1) to match the updated protocol. • Updated Section 3.5.2.1 to consistently use 2.0 cm instead of a mix of 2.0 and 2.5 (no change to the meaning of the text). • Updated text (in Section 3.5.2) to clarify that only an investigator can classify a fever as Grade 4. • Updated the evaluable infant population (in Section 4) to remove infants receiving extensive transfusions. • Updated Section 5.1 to replace Hochberg multiplicity adjustment references with Bonferroni references per CBER feedback.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Updated Sections 6.3.1.10 and 6.3.2.2.1 to remove the 50% references regarding serum neutralizing titers in order to match updated protocol. • Removed Appendix 1 Multiplicity Correction Strategy as it is no longer needed since the Bonferroni procedure will be used.
3/ 28 May 2021	Protocol amendment 4, 22 Mar 2021	• Updated different sections to match protocol amendment 4.	• Added a new secondary objective (in Section 2.1.2.1) as per the amended protocol. • Updated the endpoint related to the incidence of MA-LRTI due to RSV (in Section 2.1.3.1) to match the amended protocol. • Added a new endpoint related to analyses in premature infants (in Section 2.1.3.1) as per the amended protocol. • Added a new estimand for MA-LRTI due to RSV occurring up to 210 days, 240 days, 270 days, and 360 days (in Section 2.1.5.1) as per the amended protocol. • Added clarification for sample size in Section 2.2 and a note for the adolescent maternal participants to match the amended protocol. • Updated the 2 secondary endpoints to extend the timing of the analysis to 360 days after birth and added a new endpoint for MA-LRTI due to RSV after

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			180 days and up to 360 days in Section 3.2.1 to match the amended protocol. • Updated the endpoint related to MA-LRTI due to RSV and added a new endpoint for premature infants to Section 3.3.1. • Added clarification throughout Section 3.5.2 about reaching out to the participant's parent(s)/legal guardian (if a minor). • Updated Section 6.1.3.1 and Section 6.1.3.2 to remove analyses that were not presented in other studies in the program. • Updated Section 6.2.1.1.1 to add the time point at 360 days. • Added Section 6.2.1.3 for the new secondary endpoint. • Updated Section 6.3.1.4 for the period of the analysis. • Updated to mention all time points included (120, 150, and 180 days) in Section 6.1.1.2.1, Section 6.2.1.1.1, and Section 6.3.1.1. • Added Section 6.3.1.13 for the analyses on premature babies. • Updated Table 10 by removing the efficacy subgroup analyses by time from vaccination to delivery, changing the population for the immunogenicity endpoints for the same

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			subgroups, adding some clarification for the pregnancy outcome, adding new subgroup analyses by age at vaccination (to match the updated protocol), changing name of a subgroup from "time of enrollment" to "duration of planned follow-up" (same groups), and removing the groups for income-level subgroup analyses. • Updated Appendix 1 as AESI category is now collected in the CRF. • Updated Section 6.5.11 to add GA at vaccination categories in the demographic variables to be presented. • Updated Section 6.6.5 to add GA at birth categories. • Removed former Appendix 2 and added the URL for the source website in the reference section. • Removed 1 reference as it was only mentioned in an appendix that was deleted.
4/ 13 Oct 2021	Protocol amendment 4, 22 Mar 2021	• Updated different sections to make the exclusions endpoint specific.	• Updated the primary and secondary estimands (in Section 2.1.4 and Section 2.1.5) related to intercurrent events to account for removing events that happen after an extreme transfusion or administration of palivizumab/another monoclonal antibody therapy targeting RSV.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Updated Section 2.1.4.1 to specify that severe MA-LRTIs due to RSV positive adjudicated cases will be programmatically derived as MA-LRTI due to RSV. • Updated Section 4 to remove the reference to the data handling memo as a result of a process change. • Updated Section 4 to remove from the evaluable efficacy – infant population definition extreme transfusion and administration of palivizumab/another monoclonal antibody therapy targeting RSV (to make these exclusion endpoint–specific). • Updated Table 8 to explain that all severe MA-LRTIs due to RSV are a subset of MA-LRTI due to RSV. • Updated Section 6.1.1.1.1, Section 6.1.1.2.1, Section 6.2.1.1.1, Section 6.2.1.3.1, Section 6.3.1.1, Section 6.3.1.2, Section 6.3.1.8, and Section 6.3.1.13 in the analysis portion to specify that cases after extreme transfusion or administration of palivizumab/another monoclonal antibody therapy targeting RSV will be excluded.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Updated Section 6.5.1.1 for the GA at vaccination categories to include a new category (“>36 weeks”) and revised the “≥32 to <36 weeks” category to “≥32 to ≤36 weeks” to include 36 weeks. • Removed the text on NDCMC-specific terms from Section 6.6.1 and added a reference regarding summary and listings data generation in Section 6.6.6 (as only 1 combined output with 2 different sources will be required). • Updated Section 6.3.1.9 to add more specifics for an analysis of non–RSV-positive pathogens only using RSV-positive adjudicated MA-LRTI cases. • Updated Table 10 to change the categories of the “Time since vaccination to delivery” variable, to combine the previous 2 categories. • Updated Table 10 to add subgroup analyses by gender and race as per CBER request. • Updated Section 6.6.3 to a flexible language as it is not sure these outputs will be required.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Updated Section 7.1 and Section 7.2 to allow the DMC members to look at severe cases at the interim analysis from a safety perspective.
5/ 31 Mar 2022	Protocol amendment 5, Jan 2022	• Updated sensitivity/supplementary analysis per CBER request. • Updated interim analysis section to follow PA5.	• Added Section 5.3.3 to describe management of missing data in efficacy analysis as per CBER request. • Updated Section 6.1.1.1.2 to specify the analysis addressing the issue of missing swabs. • Updated Section 6.2.1.1.2 with additional details for an analysis that was requested by CBER. • Updated language in Section 7.2 to include the possibility of having 2 interim analyses and to specify the minimum number of cases for this analyses. • Updated Section 7.2 with more details about alpha levels to be used for efficacy endpoints. • Updated Table 11 to show examples for vaccine efficacy at both potential interim analyses (at 43 and 62 cases).
6/ 02 Sep 2022	Protocol amendment 7, 08 Aug 2022	• Updated sensitivity/supplementary analysis per CBER request. • Updated the interim analysis section to follow PA7.	• Removed the IgG1 endpoint from Section 3.3.2 as per PA7. • Updated Section 5.3.2 to specify that some LLOQ values might not be in the table.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Updated Section 6.1.1.1.2 to include the expanded swab analysis, the imputed missing swab analysis, and the combined Phase 2 and 3 efficacy analysis. • Updated Section 6.1.1.2.2 to add the imputed missing swab analysis and combined Phase 2 and 3 efficacy analysis. • Updated Section 6.3.2.3 to remove all references to IgG1. • Updated Section 6.4 to allow for the analysis of a subset of immunogenicity results. • Updated Section 7.2 as per the updated protocol and CBER feedback. • Updated Table 11 as per the updated protocol.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671008. 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 endpoints, followed by details of statistical reporting. A list of tables, listings, and figures, mockup shells, 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.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Primary Objectives

2.1.1.1. Primary Efficacy Objectives – Infant Participants

- To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.
- To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.

2.1.1.2. Primary Safety Objective – Infant Participants

- To describe the safety of RSVpreF.

2.1.1.3. Primary Safety Objective – Maternal Participants

- To describe the safety and tolerability of RSVpreF.

2.1.2. Secondary Objectives

2.1.2.1. Secondary Efficacy Objectives – Infant Participants

- To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.
- To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.
- To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV occurring within 360 days after birth.

2.1.3. Exploratory Objectives

2.1.3.1. Exploratory Objectives – Infant Participants

- To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI due to RSV.
- To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI.
- To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV in infants after 12 months of age.
- To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV in infants after 6 months of age.
- To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV in infants after 6 months of age.
- To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI in infants after 6 months of age.

- To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTIs due to RSV A and the incidence of MA-LRTIs due to RSV B.
- To describe the non-RSV infectious etiology of MA-RTI in the study population.
- To evaluate RSV serum neutralizing titers elicited by RSVpreF and transferred transplacentally.
- To assess the impact of RSVpreF on RSV illness based on socioeconomic factors.
- To assess the effect of RSVpreF on healthcare utilization.
- To describe the efficacy of RSVpreF in reducing the incidence of MA-RTI, MA-LRTI, and severe MA-LRTI in premature infants <37 weeks of age.

2.1.3.2. Exploratory Objectives – Maternal Participants

- To describe MA-RTI in this study population.
- To evaluate the immune responses elicited by RSVpreF.

2.1.4. Primary Estimands

2.1.4.1. Primary Efficacy Estimands – Infant Participants

- **VE, defined as the RR reduction of RSV-positive MA-LRTI occurring within 90 days, 120 days, 150 days, and 180 days after birth in the RSV vaccine group compared to the placebo group.**

  This estimand includes the following 4 attributes:

  - Population: Infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable efficacy infant participants).
  - Variable: Occurrence of RSV-positive MA-LRTI within 90 days, 120 days, 150 days, and 180 days after birth as confirmed by the EAC (any adjudicated severe MA-LRTI cases due to RSV are also by definition MA-LRTI cases).
  - Intercurrent event(s): For participants who discontinue from the study or have major protocol deviations, all postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age.
  - Population-level summary: RR reduction of RSV-positive MA-LRTI occurring up to 90 days, 120 days, 150 days, and 180 days in the RSV vaccine group compared to the placebo group.

- **VE, defined as the RR reduction of severe MA-LRTI due to RSV occurring within 90 days, 120 days, 150 days, and 180 days after birth in the RSV vaccine group compared to the placebo group.**

  This estimand includes the following 4 attributes:

  - Population: Infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable efficacy infant participants).
  - Variable: Occurrence of severe MA-LRTI due to RSV occurring within 90 days, 120 days, 150 days, and 180 days after birth as confirmed by the EAC.
  - Intercurrent event(s): For participants who discontinue from the study or have major protocol deviations, all postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age.
  - Population-level summary: RR reduction of severe MA-LRTI due to RSV occurring up to 90 days, 120 days, 150 days, and 180 days in the RSV vaccine group compared to the placebo group.

2.1.4.2. Primary Safety Estimands – Infant Participants

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

  This estimand includes the following 4 attributes:

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

- **Percentage of infant participants having AEs from birth to 1 month 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 AEs from birth to 1 month.

- 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 from birth to 1 month of age in each group.

- **Percentage of infant participants with SAEs and NDCMCs from birth through 6 and 12 months.**

  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 and NDCMCs from birth through 6 and 12 months of 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 6 and 12 months of life in each group.

- **Percentage of infant participants with SAEs and NDCMCs from birth through 24 months.**

  This estimand includes the following 4 attributes:

  - Population: Infant participants born to the maternal participants enrolled during the first year of the study and who received 1 dose of investigational product.

  - Variable: Presence/absence of SAEs and NDCMCs from birth through 24 months of 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 24 months of life in each group and percentage of infant participants with the event of interest between 12 and 24 months of life in each group.

2.1.4.3. Primary Safety Estimands – Maternal Participants

- **Percentage of maternal participants reporting prespecified 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 group.

- **Percentage of maternal participants reporting prespecified 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 group.

- **Percentage of maternal participants reporting 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 group.

- **The percentage of maternal participants reporting 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 SAEs 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 SAEs throughout the study in each group.

2.1.5. Secondary Estimands

2.1.5.1. Secondary Efficacy Estimands – Infant Participants

- **VE, defined as the RR reduction of hospitalization due to RSV occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth in the RSV vaccine group compared to the placebo group.**

  This estimand includes the following 4 attributes:

  - Population: Infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable efficacy infant participants).
  - Variable: Occurrence of hospitalization due to RSV occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth as confirmed by the EAC.
  - Intercurrent event(s): For participants who discontinue from the study or have major protocol deviations, all postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age.
  - Population-level summary: RR reduction of hospitalization due to RSV occurring up to 90 days, 120 days, 150 days, 180 days, and 360 days in the RSV vaccine group compared to the placebo group.

- **VE, defined as RR reduction of MA-LRTI due to any cause occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth in the RSV vaccine group compared to the placebo group.**

  This estimand includes the following 4 attributes:

  - Population: Infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable efficacy infant participants).
  - Variable: Occurrence of MA-LRTI due to any cause occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth.
  - Intercurrent event(s): For participants who discontinue from the study or have major protocol deviations, all postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age.
  - Population-level summary: RR reduction of MA-LRTI due to any cause occurring up to 90 days, 120 days, 150 days, 180 days, and 360 days in the RSV vaccine group compared to the placebo group.

- **VE, defined as the RR reduction of MA-LRTI due to RSV occurring within 210 days, 240 days, 270 days, and 360 days after birth in the RSV vaccine group compared to the placebo group.**

  This estimand includes the following 4 attributes:

  - Population: Infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable efficacy infant participants).
  - Variable: Occurrence of MA-LRTI due to RSV occurring within 210 days, 240 days, 270 days, and 360 days after birth.
  - Intercurrent event(s): For participants who discontinue from the study or have major protocol deviations, all postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age.
  - Population-level summary: RR reduction of MA-LRTI due to RSV occurring up to 210 days, 240 days, 270 days, and 360 days in the RSV vaccine group compared to the placebo group.

2.2. Study Design

This is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study to assess the efficacy, safety, and immunogenicity of bivalent RSVpreF or placebo (1:1 randomization) in infants born to healthy women vaccinated during pregnancy, and the safety and immunogenicity in the pregnant women. This will be a global study, including sites in both the northern and southern hemispheres, and it will span multiple RSV seasons.

This is an event-driven study with a target of 124 adjudicated (primary-endpoint) cases of MA-LRTI due to RSV (meeting the case definition in the per-protocol infant population described in Section 9.2 of the protocol). Vaccination of maternal participants will occur at a time of year such that the infant is likely to be exposed to seasonal RSV during the first 6 months of life. It was anticipated that approximately 6900 mother-infant pairs would be needed to accumulate 124 per-protocol cases prior to the global COVID-19 pandemic. With the variable RSV season, the sample size may need to be increased and enrollment could go up to 10,000 maternal participants based on the number of RSV cases.

Study-eligible pregnant women will be randomized in a 1:1 ratio to receive a single dose RSVpreF or placebo. The dose of RSV prefusion F antigen in RSVpreF for this study will be 120 µg (60 µg A and 60 µg B).

Assessments for mothers will include parameters to allow descriptions of safety, tolerability, and immunogenicity of the vaccine in maternal participants.

For all infant participants, data will be collected for any medically attended respiratory illness to assess for cases of LRTI due to RSV (efficacy endpoint). Additionally, throughout the study all respiratory illnesses, SAEs, and NDCMCs reported will be assessed in this population. Infant participants enrolled during the first year of the study will be followed up for 24 months after birth, to include longer-term RTI surveillance and safety oversight to address safety and the possibility of conferred enhanced protection (antibody persistence) during a second RSV season. All other infants will be followed up for 12 months after birth. All MA-RTIs meeting the protocol definition for a potential study endpoint will be adjudicated by an independent EAC. In addition, this study will use an E-DMC to monitor vaccine safety and efficacy and study futility.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Efficacy Endpoints – Infant Participants

- RSV-positive MA-LRTI (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, and 180 days after birth (see Section 5.1 for sequence of testing across time points).

- Severe MA-LRTI due to RSV (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, and 180 days after birth (see Section 5.1 for sequence of testing across time points).

3.1.2. Primary Safety Endpoints – Infant Participants

- Specific birth outcomes.
- AEs from birth to 1 month of age.
- SAEs and NDCMCs from birth through 6 months of age.
- SAEs and NDCMCs from birth through 12 months of age.
- SAEs and NDCMCs from birth through 24 months of age (for infants born to maternal participants enrolled during the first year of the study).

3.1.3. Primary Safety 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.
- SAEs throughout the study (through the 6-month-postdelivery study visit).

3.2. Secondary Endpoints

3.2.1. Secondary Efficacy Endpoints – Infant Participants

- Hospitalization due to RSV (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth.
- MA-LRTI due to any cause with protocol-defined criteria occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth.
- RSV-positive MA-LRTI occurring within 210 days, 240 days, 270 days, and 360 days after birth.

3.3. Other Endpoints

3.3.1. Exploratory Endpoints – Infant Participants

- RSV-positive MA-RTI (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, and 180 days after birth.
- RSV-positive MA-RTI occurring 181 to 730 days after birth.
- Incidence of all-cause MA-RTIs up to 730 days after birth.
- MA-LRTIs due to RSV occurring 361 to 730 days after birth.

- Severe MA-LRTIs due to RSV occurring 181 to 730 days after birth (as confirmed by the EAC).
- Hospitalization due to RSV occurring 181 to 730 days after birth (as confirmed by the EAC).
- MA-LRTIs due to any cause occurring 181 to 730 days after birth.
- RSV subgroup A– and subgroup B–specific MA-LRTI.
- Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits.
- RSV A and RSV B serum neutralizing titers measured at birth.
- Primary and secondary efficacy by select demographic risk factors (eg, breastfeeding, maternal smoking, number of household members).
- Univariate summaries of healthcare utilization variables, which may include the following: number and type of medical visits, length of hospital stay, requirement for mechanical ventilation, requirement for respiratory diagnostic procedures, requirement for IV fluids, requirement for prescriptions, and antibiotic use.
- IgG concentrations against prefusion F measured at birth.
- MA-RTI, MA-LRTI, and severe MA-LRTI due to RSV occurring 0 to 730 days after birth in premature infants <37 weeks of age.

3.3.2. Exploratory Endpoints – Maternal Participants

- The incidence of all-cause MA-RTIs from vaccination up to 180 days after delivery.
- RSV A and RSV B serum neutralizing titers and prefusion F IgG titers measured before vaccination and at the delivery visit.
- Ig concentrations against nonvaccine RSV antigens measured before vaccination and at delivery visit.

3.4. Baseline Variables

3.4.1. 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 in infant participants: immunogenicity (cord blood sample collected at birth), physical examination, and vital signs.

3.4.2. Baseline Variables – Maternal Participants

Day 1 is defined as the day of vaccination for the maternal participants. Day 1 is considered the baseline visit for the maternal immunogenicity assessments.

Day 1 is the start of the reporting period for local reactions/systemic events. For prespecified systemic events, a baseline assessment related to the 1-week period prior to vaccination will also be recorded in the e-diary.

3.5. Safety Endpoints

3.5.1. Adverse Events

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each maternal participant, including her fetus, begins from the time the maternal participant or her parent(s)/legal guardian (if a minor) 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 28 calendar 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 nonserious AEs from informed consent through a minimum of 28 calendar days after vaccination. The active collection period for SAEs begins once informed consent has been provided until the maternal participant completes the study. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures must be reported in the CRF. Details of any MA-RTI will not be collected as an AE/SAE from informed consent until the maternal participant completes the study, unless the investigator or an appropriate designee deems the event to be possibly related to the investigational product. For maternal participants who are screen failures, the active collection period ends when screen failure status is determined.

For the infant participant, the time period for actively eliciting and collecting nonserious AEs begins at birth and continues through and including a minimum of 28 calendar days after birth. The active collection period for NDCMCs and SAEs begins at birth and continues through the last study visit. Details of any MA-RTI will not be collected as an AE/SAE from 72 hours after birth until the infant participant completes the study, unless the investigator or an appropriate designee deems the event to be possibly related to the investigational product or if it ends in death. In addition, AEs occurring up to 48 hours after blood draws or nasal swabs that are related to study procedures must be reported in the CRF.

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF and will be categorized according to the current version (at the time of reporting) of 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 NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

An ADE is defined as an AE related to the use of an investigational medical device. These events will be captured separately and reported in relation to the administration of the investigational product.

A 3-tier approach will be used to summarize AEs for maternal participants and infant participants. 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. There are currently no Tier 1 events defined.

Tier 2 events: These are events that are not Tier 1 but are "common". A MedDRA PT is defined as a Tier 2 event if there are at least 1% in at least 1 group.

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 in maternal participants, 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). Prior to vaccination, a baseline assessment of prespecified systemic events will also be recorded in the e-diary.

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 or her parent(s)/legal guardian (if a minor) 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 20 and 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 10.2.4 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 reaction is recorded as "yes" for redness or swelling with a diameter of >2.0 cm **or** "mild," "moderate," "severe," or "Grade 4" for pain at the injection site on a given day.

= "No," if the reaction is recorded as "no" **or** as "yes" with a diameter of ≤2.0 cm 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)	The reaction is reported as "yes" with a diameter of >2.0 cm for redness/swelling or "yes" for pain any day from Day 1 through Day 7.	The reaction is reported as "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on all 7 days or as a combination of "No" and missing on all 7 days.	The reaction is reported 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)	The reaction is reported as any redness or swelling >2.0 cm or "yes" for pain at injection site on any day during Days 1 through 7.	The reaction is reported as 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.	All of the local reactions are reported 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 or her parent(s)/legal guardian (if a minor). 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 all reactions are reported 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 the participant or her parent(s)/legal guardian (if a minor) 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

Prior to vaccination on Day 1, a baseline assessment of fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain will be recorded in the e-diary. Systemic events reported for Days 1 to 7 following vaccination via the e-diary are fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain. The participant or her parent(s)/legal guardian (if a minor) 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.

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 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 10.2.4 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 or her parent(s)/legal guardian (if a minor). 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 ≥38.0°C (≥100.4°F). 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 temperature grading scale displayed in Table 6.

Table 6. Grading Scale for Fever

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

a. Only an investigator or qualified designee is able to classify a maternal participant's fever as Grade 4, after clinical evaluation of the maternal participant, documentation from another medically qualified source (eg, emergency room or hospital record), or contact with the maternal participant or her parent(s)/legal guardian (if a minor). Grade 4 fevers will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.4 of the protocol.

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 a temperature ≥38.0°C for fever **or** "mild," "moderate," "severe," or "Grade 4" for the remaining events are reported on a given day.

= "No," if a temperature <38.0°C for fever **or** "none" for the remaining events are reported 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. Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
4. Maximum severity of each 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.

3.5.3. Physical Examination, Including Vital Signs

3.5.3.1. Physical Examination, Including Vital Signs: Maternal Participants

Physical examination will be performed at the screening visit 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 and recorded in the CRF.

3.5.3.2. Physical Examination, Including Vital Signs: Infant Participants

The physical examination will be performed at all scheduled in-clinic 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.

Temperature, heart rate, and respiratory rate as well as oxygen saturation by pulse oximetry will be assessed at birth, at 1 month of age, and during the active RSV surveillance procedures.

3.5.4. Obstetric Examination

Obstetric history and examination findings will be collected at the vaccination visit. The assessments will include, but not be limited to, number of pregnancies, cesarean deliveries, spontaneous abortions, ectopic pregnancies, number of preterm deliveries, GA at vaccination, 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 delivery), cesarean type (elective, semielective, emergency), the use of any assisted devices (forceps or vacuum), delivery complications (yes, no), number of births, outcome at delivery (live delivery, stillbirth, induced/elective abortion), gross visual inspection of the aborted fetus/stillbirth (not done, no observed abnormalities, observed abnormalities), and fetal pathology performed (yes, no). In addition, if information is available, group B streptococcal colonization status will also be collected along with any intrapartum antibiotic prophylaxis.

3.5.5. Birth Outcome: Infant Participants

Infant outcome at birth will be collected at the delivery visit and includes the following: GA (weeks, days); Apgar score at 1, 5, and 10 minutes; infant cry immediately after delivery (yes, no); infant suckle shortly after delivery (yes, no); and infant outcome (normal, congenital malformation/anomaly, other neonatal problem or unknown). 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 (30 days) after birth.

3.6. Health Economics

3.6.1. Healthcare Resource Utilization: Infant Participants

Details of healthcare resource utilization for all infants will be assessed at each MA-RTI visit from 72 hours after birth through the last study visit (730 days after birth). The variables collected will include the following: number, type (eg, respiratory, RAD/asthma/wheezing), and setting (eg, outpatient, urgent care, emergency room, hospitalization, ICU) of healthcare visits, length of hospital stay, requirement for mechanical ventilation (yes/no, total number of mechanical ventilation episodes, total number of hours/days on mechanical ventilation), requirement for respiratory diagnostic procedures (eg, chest radiograph, supplemental oxygen, pulse oximetry), requirement for IV fluids, requirement for prescriptions (eg, total number of prescriptions, selected respiratory medications [eg, bronchodilators, corticosteroid therapy, racemic epinephrine]), and antibiotic use (eg, total number of prescriptions, number of antibiotic use days).

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 IRT system.
Evaluable efficacy – infant (per-protocol)	All infant participants who are born to maternal participants who did not have major protocol deviations prior to the delivery and who received the investigational product to which they were randomized at least 14 days prior to delivery, are eligible, and have no major protocol deviations.
mITT efficacy – infant	All infant participants who are born to vaccinated maternal participants.
Evaluable immunogenicity – infant	All infant participants who are born to maternal participants who did not have major protocol deviations prior to the delivery and who received the investigational product to which they were randomized, are eligible, have blood drawn for assay testing within the specified time frame,[a] have valid and determinate assay results for the proposed analysis, and have no major protocol deviations.
Evaluable immunogenicity – maternal	All maternal participants who are eligible, receive the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame,[b] have valid and determinate assay results for the proposed analysis, and have no major protocol deviations.
mITT immunogenicity – 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.
mITT immunogenicity – maternal	All randomized maternal participants who receive investigational product and have at least 1 valid and determinate assay result for the proposed analysis.
Safety – infant	All infant participants who are born to vaccinated maternal participants.
Safety – maternal	All randomized maternal participants who receive investigational product.

a. A cord blood sample must be obtained on the day of birth. If cord blood is unavailable, a venous blood sample may be collected from the infant preferably within 24 hours but up to 7 days after birth.

b. The blood sample must be obtained preferably before the delivery. In the event that the blood sample cannot be obtained before delivery, the sample should be collected as close to delivery as possible and at most 48 hours postpartum.

Major protocol deviations will be determined by clinical review and identified before any immunogenicity or efficacy analysis is carried out. A major protocol deviation is a protocol violation that, in the opinion of the study clinician medical monitor, would materially affect assessment of immunogenicity or 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.

5. GENERAL METHODOLOGY AND CONVENTIONS

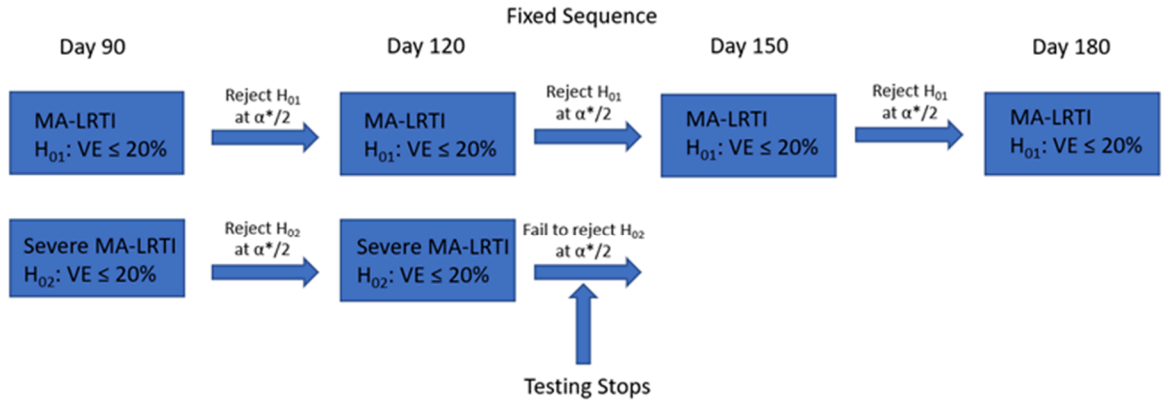
5.1. Hypotheses and Decision Rules

The null hypothesis to be tested concerns VE for the primary endpoints. RSVpreF will be compared to placebo, testing the hypotheses for each endpoint of H_{0i}: VE $\leq$20% vs H_{ai}: VE >20%, where i = 1 denotes the MA-LRTI endpoint and i = 2 denotes the severe MA-LRTI endpoint. The overall primary null hypothesis is then $H_0 = H_{01} \cap H_{02}$. For all secondary efficacy endpoints, RSVpreF will be compared to placebo, testing the hypotheses H_0: VE $\leq$0% vs H_a: VE >0%. Hypothesis testing of the secondary endpoints is conditional upon rejection of the null hypothesis for at least 1 of the primary endpoints.

The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV will be tested in parallel using a Bonferroni multiplicity adjustment procedure, whereby half the available alpha is used on each of the 2 endpoints. Success of the trial requires rejection of the null hypothesis (ie, a CI lower bound >20%) for either of the 2 primary endpoints.

Testing of the 2 primary endpoints across the time intervals will follow a fixed sequence with a gatekeeping strategy. First, the hypothesis pertaining to the incidence of the 2 primary endpoints within 90 days after birth will be tested, at the full multiplicity-adjusted alpha level, using a Bonferroni adjustment. If the null hypothesis for both of the endpoints cannot be rejected, testing ends. Otherwise, testing proceeds with the incidence within 120 days after birth. Only primary endpoint(s) that are successful at all earlier time intervals will be considered at subsequent intervals. Testing will proceed to the endpoints evaluated at 150 days and 180 days, conditional on rejection of the null hypotheses for all earlier time intervals. In Figure 1 a possible testing flow for the 2 primary endpoints at the final analysis is presented.

Figure 1. Example of Possible Testing Flow for Primary Endpoints at Final Analysis



Abbreviations: H_{01} = null hypothesis for the MA-LRTI endpoint; H_{02} = null hypothesis for the severe MA-LRTI endpoint; MA-LRTI = medically attended lower respiratory tract illness; VE = vaccine efficacy.

Inference for the secondary endpoints will be conditional upon demonstrating success through 180 days for 1 of the primary efficacy endpoints. The secondary endpoints of hospitalizations due to RSV, all-cause MA-LRTI, and MA-LRTI beyond 180 days will be tested in parallel so as to preserve the overall type I error across primary and secondary endpoint families at no more than 2.5% 1-sided. The alpha level available for the secondary endpoints will be dependent upon the results of the primary endpoints. If both primary endpoints are successful through 180 days, the full alpha will be available for the secondary endpoints. If only 1 of the 2 primary endpoints is successful through 180 days, half the alpha will be available. A Bonferroni multiplicity adjustment will also be used to analyze the 3 secondary endpoints in parallel. VE will be evaluated sequentially at 90 days, 120 days, 150 days, 180 days, and 360 days for hospitalization due to RSV and all-cause MA-LRTI and at 210 days, 240 days, 270 days, and 360 days for MA-LRTI due to RSV. In addition, the same fixed-sequence testing and gatekeeping strategy used for the primary endpoints will be employed.

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 percentage (%) and the n (the numerator) and N (the denominator) used in the calculation of the percentage.

All data will be summarized by vaccine group of the maternal participants. 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 serum neutralizing titers.

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 analysis of efficacy will use a conditional exact test[1] based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. The number of cases $x_i \sim P(\lambda_i)$, where P() is the Poisson distribution ($i = 1$ denotes placebo, $i = 2$ denotes vaccine). It is known that $x_2|T = t \sim B(T, \pi)$, where B() is the binomial distribution, $T = x_1 + x_2$ (the total number of events), and $\pi = \lambda_2/(\lambda_1 + \lambda_2)$. Then, assuming equal numbers of participants per group, testing the hypothesis H_0: $VE \leq \theta$ is equivalent to testing H_0: $\pi \geq (1 - \theta)/(2 - \theta)$.

The 95% CI for proportions will be constructed by the Clopper-Pearson method described by Newcombe.[2] The 95% CI will be presented in terms of percentage.

The 95% CI for differences in the proportions will be computed using the Miettinen and Nurminen method.[3] 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

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. The GMT and associated 2-sided 95% CI will be calculated at each available time point for each group. 95% CI for GMT will be obtained by exponentiating the limits 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

The GMFR will be calculated by exponentiating the mean difference of an individual participant's logarithmically transformed titer levels (postvaccination minus prevaccination). 95% CI will be obtained by exponentiating the limits of the 95% CI for the mean difference of the logarithmically transformed assay results using Student's t distribution.

5.2.2.3. Geometric Mean Ratio

The GMR will be calculated by exponentiating the group mean difference of logarithmically transformed titer levels. 95% CI will be obtained by exponentiating the limits of the CIs for the mean difference of the logarithmically transformed assay results using Student's t distribution.

5.2.2.4. Reverse Cumulative Distribution Curves

RCDCs for RSV A and RSV B serum neutralizing titers for a combination of available time points and vaccine groups will be generated.

5.3. Methods to Manage Missing 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. 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 the 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 < LLOQ will be converted to a value of ½ LLOQ (LLOQ values for each assay are presented in Table 7). Serology data transfers will include LLOQ values applicable to all assays reported, and may supersede the values shown here. 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 1 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 > ULOQ will be converted to a value of ULOQ.

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

Table 7. LLOQ Values

Assay	LLOQ Value
RSV A 50% serum neutralizing titer	50
RSV B 50% serum neutralizing titer	70
RSV A 90% serum neutralizing titer	50
RSV B 90% serum neutralizing titer	55
Anti–RSV A prefusion F IgG	2.620
Anti–RSV B prefusion F IgG	2.620
Anti-Ga RSV nonvaccine-antigen Ig	0.490
Anti-Gb RSV nonvaccine-antigen Ig	0.490
Anti-M RSV nonvaccine-antigen Ig	0.490
Anti-N RSV nonvaccine-antigen Ig	0.550

Abbreviations: Ig = immunoglobulin; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; RSV A = respiratory syncytial virus subgroup A; RSV B = respiratory syncytial virus subgroup B.

5.3.3. Efficacy Data

Cases that qualify as MA-LRTI events based on clinical signs and symptoms but do not have a valid RSV swab result will be identified. Sensitivity analyses of the primary endpoints will be done under various assumptions about the missing swab results. In each scenario, cases with imputed positive RSV results will be added to the confirmed RSV-positive cases and vaccine efficacy in the augmented set of cases analyzed.

Based on a blinded review of swab results at the end of February 2022, approximately 22% of all swabs from MA-LRTI events with valid central lab results cases proved to be RSV-positive. Thus, a minority of the missing results are expected to be truly RSV-positive, and imputation scenarios will include:

- Missing swab results are assumed to be positive in the same proportion (by vaccine group) as the nonmissing swab results in MA-LRTI events (missing-at-random assumption).

- For the vaccine group, missing swab results are assumed to be positive in higher proportions than the nonmissing swab results in MA-LRTI events, while in the placebo group missing swab results are assumed to be positive in the same proportion as the nonmissing swab results in MA-LRTI events (missing-not-at-random assumption). A range of higher vaccine group positivity rates will be assumed.

Multiple imputations will be performed to randomly assign missing swab results. SAS PROC MI will be used to generate 500 imputed data sets for each scenario. Mean and median VE across imputations, and the proportion of imputations with VE lower bound >20% will be reported.

5.4. Endpoint Events and Definitions

5.4.1. Endpoint Events and Definitions – Infant Participants

The study endpoints for infant participants employ the event definitions in Table 8.

Table 8. Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoint/Assessment	Study Definition
Medically attended visit	Infant participant has been taken to or seen by a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit).
MA-RTI visit for infant participant	A medically attended visit AND 1 or more of the following RTI signs and symptoms: • Nasal discharge for 24 hours or more • Difficulty breathing, labored breathing, or rapid breathing for any duration • Cough • Inability to feed for any duration because of respiratory symptoms • Apnea • Any other respiratory symptom of concern
RSV-positive test[a]	• RSV RT-PCR–positive test result by Pfizer central laboratory **OR** • RSV-positive test result by certified[b] laboratory with NAAT for RSV
MA-RTI due to RSV[a]	• An MA-RTI visit **AND** • RSV-positive test result as described in Section 8.1.1.1 of the protocol
MA-LRTI due to any cause	• Infant with an MA-RTI visit **AND** • Fast breathing (respiratory rate ≥60 bpm for <2 months of age [<60 days of age], ≥50 bpm for ≥2 months to < 12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <95% **OR** • Chest wall indrawing

Table 8. Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoint/Assessment	Study Definition
MA-LRTI due to RSV[a]	• Infant with an MA-RTI visit **AND** • Fast breathing (respiratory rate ≥60 bpm for <2 months of age [<60 days of age], ≥50 bpm for ≥2 months to < 12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <95% **OR** • Chest wall indrawing **AND** • RSV-positive test result as described in Section 8.1.1.1 of the protocol
Hospitalized RTI due to RSV[a]	• An RTI due to RSV that results in hospitalization
Severe MA-LRTI due to RSV[a]	• Infant with an MA-RTI visit **AND** • Fast breathing (respiratory rate ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for ≥2 months to < 12 months of age, or ≥50 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <93% **OR** • High-flow nasal cannula or mechanical ventilation (invasive or noninvasive) **OR** • ICU admission for >4 hours **OR** • Failure to respond/unconscious **AND** • RSV-positive test result as described in Section 8.1.1.1 of the protocol
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by EAC[c]

Abbreviations: EAC = endpoint adjudication committee; ICU = intensive care unit; MA-LRTI = medically attended lower respiratory tract illness; MA-RTI = medically attended respiratory tract illness; NAAT = nucleic acid amplification test; RSV = respiratory syncytial virus; RTI = respiratory tract illness; RT-PCR = reverse transcription–polymerase chain reaction; SpO_2 = oxygen saturation as measured by pulse oximetry.

a. The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTI and RTI study visits, including all available RSV test results.
b. See the EAC charter for more details regarding the certified laboratory.
c. Severe MA-LRTI cases that are adjudicated by the EAC will always be MA-LRTI cases (severe MA-LRTIs are a subset of the MA-LRTIs).

5.4.2. Endpoint Events and Definitions – Maternal Participants

The study endpoints for maternal participants employ the event definitions in Table 9.

Table 9. Endpoint Events and Definition in Maternal Participants

Study Endpoint/Assessment	Study Definition
Maternal medically attended visit	The maternal participant reports a visit with a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit).
MA-RTI visit for maternal participant	A medically attended visit AND 1 or more of the following RTI signs and symptoms: • New or increased sore throat • New or increased cough • New or increased nasal congestion • New or increased nasal discharge • New or increased wheezing • New or increased sputum production • New or increased shortness of breath

Abbreviations: MA-RTI = medically attended respiratory tract illness; RTI = respiratory tract illness.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Efficacy Endpoints – Infant Participants

6.1.1.1. RSV-Positive MA-LRTI (as Confirmed by the EAC) Occurring Within 90 Days, 120 Days, 150 Days, and 180 Days After Birth

6.1.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Evaluable efficacy – infant (Section 4).
- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups.
- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age.
- For each group, the number (n), percentage, and 95% CI of RSV-positive MA-LRTI cases occurring within 90 days, 120 days, 150 days, and 180 days after birth, as confirmed by the EAC, will be presented for each group. Severe MA-LRTI cases are a subset of MA-LRTI cases, and all severe MA-LRTI cases will also be considered MA-LRTI cases.

- VE compared to placebo along with the corresponding 100(1- alpha)% CI (adjusted for the interim) will be presented. This will be based on raw numbers of cases and also with an adjustment for any differences in follow-up time. See Section 5.1 for testing procedures.

- Kaplan-Meier curves showing accrual of cases for this endpoint over 180 days will be presented.

6.1.1.1.2. Supplementary Analysis

The main analysis will also be performed based on the mITT efficacy infant population. Other supportive analyses will address the impact of specific issues, as follows.

Impact of palivizumab administration: A supportive analysis of the primary endpoint will be performed to address the potential intercurrent event of palivizumab administration via a composite estimand strategy. For this analysis, the population will be the mITT efficacy infant set. The endpoint analyzed will be the occurrence of either MA-LRTI due to RSV (as defined for the main analysis) or receipt of palivizumab. VE with respect to this outcome will be estimated in the same way as for the main analysis.

Imputed missing swab analysis: Where MA-LRTI and severe MA-LRTI visits have no accompanying valid central or local NAAT test results, positive or negative results will be imputed as described in Section 5.3.3. If any such events were adjudicated, only those that were confirmed by the EAC as MA-LRTI or severe MA-LRTI will undergo imputation. The imputed RSV-positive cases will be added to the per-protocol cases and VE estimated in the same way as for the main analysis.

Expanded swab analysis: Where some evidence of RSV positivity exists from MA-LRTI and severe MA-LRTI visit swabs, any test indicating positivity for RSV will be accepted and used to define MA-LRTI cases whenever the clinical symptoms qualify. Examples of positive swab results that do not count for the primary endpoint definition, but will be counted in this analysis, are local non-NAAT tests, central laboratory PCR tests from samples taken outside the protocol-specified window, and centrally-tested swabs that exceeded the documented stability testing duration but were positive. Where events were adjudicated, the committee's decision on the event as MA-LRTI or severe MA-LRTI will be used; if not adjudicated, the event will be assessed according to the protocol criteria for each event. VE including these additional RSV-positive cases will be estimated in the same way as for the main analysis.

Combined analysis of Phase 2b/Phase 3 efficacy data: In order to provide additional summaries of RSVpreF VE, combined data from Studies C3671003 and C3671008 (this study) will be generated for descriptive purposes only. Data on incidence of MA-LRTI and severe MA-LRTI will be combined using the Phase 3 endpoint definitions. The 4 RSVpreF groups in the C3671003 study will be combined. VE will be estimated by simple pooling of the study data without stratification/weighting, and 95% CI provided. The analysis will be considered final after all infants in both studies have reached 180 days of age.

6.1.1.2. Severe MA-LRTI Due to RSV (as Confirmed by the EAC) Occurring Within 90 Days, 120 Days, 150 Days, and 180 Days After Birth

6.1.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Evaluable efficacy – infant (Section 4).
- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups.
- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age. For each group, the number (n), percentage, and 95% CI of cases of severe MA-LRTI due to RSV occurring within 90 days, 120 days, 150 days, and 180 days after birth (as confirmed by the EAC) will be presented for each group.
- VE compared to placebo along with the corresponding 100(1 - α)% CI (adjusted for the interim) will be presented. This will be based on raw numbers of cases and also with an adjustment for any differences in follow-up time. See Section 5.1 for testing procedures.
- Kaplan-Meier curves showing accrual of cases for this endpoint over 180 days will be presented.

6.1.1.2.2. Supplementary Analysis

The main analysis will also be performed based on the mITT efficacy infant population. Furthermore, an analysis with missing swab imputation and the efficacy analysis on combined data from Phases 2 and 3 similar to those mentioned in Section 6.1.1.1.2 will be performed for this endpoint as well.

6.1.2. Primary Safety Endpoints: Infant Participants

6.1.2.1. Specific Birth Outcomes

- Analysis set: Safety – infant (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, the number and proportion of participants with each specific birth outcome (see Appendix 1 for the list of specific birth outcomes) will be presented by vaccine group. In addition, the 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 – infant (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. No Tier 1 events are identified.

- 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, the number of participants with AEs within 1 month of age (30 days) (n), percentage, 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, the difference in proportions and associated 2-sided 95% CI between the vaccine group and the placebo group will be presented.

6.1.2.3. SAEs and NDCMCs From Birth Through 6 and 12 Months of Age

- Analysis set: Safety – infant (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, the number of participants with SAEs and NDCMCs through 6 and 12 months of age (n), percentage, and 95% CI will be presented (in separate outputs) for any event, each SOC, and each PT within each SOC, by vaccine group.

6.1.2.4. SAEs and NDCMCs From Birth Through 24 Months of Age (for Infants Born to Maternal Participants Enrolled During First Year of the Study)

- Analysis set: Safety – infant (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, the number of participants with SAEs and NDCMCs (in separate outputs) through 24 months of age (n), percentage, and 95% CI will be presented for any event, each SOC, and each PT within each SOC, by vaccine group.

- For each group, the number of participants with SAEs and NDCMCs (in separate outputs) between 12 and 24 months of age (n), percentage, and 95% CI will be presented for any event, each SOC, and each PT within each SOC, by vaccine group.

6.1.3. Primary Safety Endpoints: Maternal Participants

6.1.3.1. Local Reactions Within 7 Days After Vaccination

- Analysis set: Safety – maternal (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, percentage, and 95% CI will be presented by vaccine group for the following variables (additional variables might be added depending on team's decision):

  - Presence or absence of any local reaction on each day (Days 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.

6.1.3.2. Systemic Events Within 7 Days After Vaccination

- Analysis set: Safety – maternal (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, percentage, and 95% CI will be presented by vaccine group for the following variables (additional variables might be added depending on team's decision):
    - Presence or absence of any systemic event on each day (Days 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.

6.1.3.3. AEs Within 1 Month After Vaccination

- Analysis set: Safety – maternal (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. No Tier 1 events are identified.
- 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, the number of participants with AEs within 1 month (30 days) after vaccination (n), percentage, 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, the difference in proportions and associated 2-sided 95% CI between the vaccine group and the placebo group will be presented.

6.1.3.4. SAEs Throughout the Study

- Analysis set: Safety – maternal (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, the number of participants with SAEs throughout the study (n), percentage, and 95% CI will be presented for any event, each SOC, and each PT within each SOC, by vaccine group.

6.2. Secondary Endpoints

6.2.1. Secondary Efficacy Endpoints – Infant Participants

6.2.1.1. Hospitalization Due to RSV (as Confirmed by the EAC) Occurring Within 90 Days, 120 Days, 150 Days, 180 Days, and 360 Days After Birth

6.2.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.

- Analysis set: Evaluable efficacy – infant (Section 4).

- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups.

- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age. For each group, the number (n), percentage, and 95% CI of cases of hospitalization due to RSV occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth as confirmed by the EAC will be presented.

- VE compared to placebo along with the 95% CI will be presented. This will be based on raw numbers of cases and also with an adjustment for any differences in follow-up time. The analyses up to 120 days, 150 days, 180 days, and 360 days will be performed if previous analysis for each interval meets the efficacy criteria.

- Kaplan-Meier curves showing accrual of cases for this endpoint over 360 days will be presented.

6.2.1.1.2. Supplementary Analysis

The main analysis will also be performed based on the mITT efficacy infant population. In addition, an analysis including only hospitalization cases that also had ICU admission will be conducted in the evaluable for efficacy population.

6.2.1.2. MA-LRTI Due to Any Cause With Protocol-Defined Criteria Occurring Within 90 Days, 120 Days, 150 Days, 180 Days, and 360 Days After Birth

All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.2.1.1.

6.2.1.3. RSV-Positive MA-LRTI Occurring Within 210 Days, 240 Days, 270 Days, and 360 Days After Birth

6.2.1.3.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Evaluable efficacy – infant (Section 4).
- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups.
- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored; such events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age. For each group, the number (n), percentage, and 95% CI of RSV-positive MA-LRTI cases occurring within 210 days, 240 days, 270 days, and 360 days after birth will be presented.
- VE compared to placebo along with the 95% CI will be presented. This will be based on raw numbers of cases and also with an adjustment for any differences in follow-up time. The analyses up to 240 days, 270 days, and 360 days will be performed if previous analysis for each interval meets the efficacy criteria.
- Kaplan-Meier curves showing accrual of cases for this endpoint over 360 days will be presented.

6.3. Other Endpoints

6.3.1. Exploratory Endpoints: Infant Participants

6.3.1.1. RSV-Positive MA-RTI (as Confirmed by the EAC) Occurring Within 90 Days, 120 Days, 150 Days, and 180 Days After Birth

- Analysis set: Evaluable efficacy – infant (Section 4).
- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. Events that happen after the infant received palivizumab or another monoclonal antibody targeting RSV or after he/she had transfusions of more than 20 mL/kg of any blood products at ≤180 days of age will be excluded. For each group, the number (n), percentage, and 95% CI of RSV-positive MA-RTI cases occurring within 90 days, 120 days, 150 days, and 180 days after birth will be presented for each group.
- VE compared to placebo along with the 95% CI will be presented. The analyses up to 120 days, 150 days, and 180 days will be performed if previous analysis for each interval meets the efficacy criteria.

- Kaplan-Meier curves showing accrual of cases for this endpoint over 180 days will be presented.

6.3.1.2. RSV-Positive MA-RTI Occurring 181 to 730 Days After Birth

- Analysis set: Evaluable efficacy – infant (Section 4).

- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. Events that happen after the infant received palivizumab or another monoclonal antibody targeting RSV or after he/she had transfusions of more than 20 mL/kg of any blood products at ≤180 days of age will be excluded.

- For each group, the number (n), percentage, and 95% CI of RSV-positive MA-RTI cases occurring within 181 to 730 days will be presented for each group.

- For each group, the number (n), percentage, and 95% CI of RSV-positive MA-RTI cases occurring within 361 to 730 days will be presented for each group (just for the participants enrolled in the first year of the study).

- VE compared to placebo along with the 95% CI will be presented for each analysis interval separately.

6.3.1.3. Incidence of All-Cause MA-RTIs Up to 730 Days After Birth

The interval of interest for this analysis is up to 730 days after birth. All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.3.1.2.

6.3.1.4. MA-LRTIs Due to RSV Occurring 361 Days to 730 Days After Birth

The interval of interest for this analysis is 361 to 730 days after birth. All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.3.1.2.

6.3.1.5. Severe MA-LRTIs Due to RSV (as Confirmed by the EAC) Occurring 181 Days to 730 Days After Birth

The interval of interest for this analysis is 181 to 730 days after birth. All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.3.1.2.

6.3.1.6. Hospitalization Due to RSV (as Confirmed by the EAC) Occurring 181 to 730 Days After Birth

The interval of interest for this analysis is 181 to 730 days after birth. All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.3.1.2.

6.3.1.7. MA-LRTIs Due to Any Cause Occurring 181 to 730 Days After Birth

The interval of interest for this analysis is 181 to 730 days after birth. All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.3.1.2.

6.3.1.8. RSV Subgroup A– and Subgroup B–Specific MA-LRTI (as Confirmed by the EAC) Occurring Within 180 Days After Birth

- Analysis set: Evaluable efficacy – infant (Section 4).

- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. Events that happen after the infant received palivizumab or another monoclonal antibody targeting RSV or after he/she had transfusions of more than 20 mL/kg of any blood products at ≤180 days of age will be excluded.

- For each group, the number (n), percentage, and 95% CI of RSV subgroup A–and subgroup B–specific MA-LRTI cases occurring within 180 days (as confirmed by the EAC or RSV-positive severe MA-LRTI adjudicated cases) will be presented for each group (only RSV positivity from the Pfizer central laboratory will be considered; RSV-positive results from local tests that have no corresponding VRD-confirmed positive result will be considered to be in an RSV subgroup of "indeterminate").

- VE in the RSV vaccine group compared to the placebo group along with the 95% CI will be presented.

6.3.1.9. Positivity for Non-RSV Pathogens Obtained at MA-RTI Visits Occurring Within 180 Days After Birth

- Analysis set: Evaluable efficacy – infant (Section 4).

- Analysis methodology: Descriptive summary statistics.

- For each group, the number and percentage of participants with positive non-RSV respiratory pathogen results (from local tests) will be presented.

- For each group, the number and proportion of participants with positive non-RSV respiratory pathogens (from nasal swabs collected at an RTI study visit and tested by the Pfizer central laboratory for a panel of target pathogens, including SARS-CoV-2) will be presented. In addition, a separate analysis using RSV-positive adjudicated MA-LRTI cases might be presented separately.

6.3.1.10. RSV A and RSV B Serum Neutralizing Titers Measured at Birth

- Analysis set: Evaluable immunogenicity – infant (Section 4).

- Analysis methodology: Descriptive summary statistics. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed. Only samples tested by the Pfizer central laboratory will be considered for this analysis.

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

- GMTs of the combined RSV A/B serum neutralizing titer 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 serum neutralizing titers will be calculated, along with associated 2-sided 95% CIs.

- GMR of the RSV vaccine group to the placebo group for the combined RSV A/B serum neutralizing titers will be calculated, along with associated 2-sided 95% CIs.

- Geometric means of the placental transfer ratio and associated 2-sided 95% CIs will be provided for RSV A, RSV B, and combined RSV A/B serum neutralizing titers. For each mother-infant dyad, the transfer ratio will be calculated as the ratio of the infant's RSV serum neutralizing titer at birth to the mother's RSV serum neutralizing titer at delivery. Group geometric means and CIs are calculated in the same way as for similar endpoints using the fold rise calculated above.

- A correlation scatterplot will be generated, with the infant blood titer on the x-axis and maternal titer on the y-axis.

6.3.1.11. Healthcare Resource Utilization

6.3.1.11.1. Main Analysis

- Analysis set: Safety population – infant (Section 4).

- Analysis methodology: Univariate summaries of healthcare resource utilization variables will be compared between the RSVpreF and placebo groups.

- For categorical variables (type and setting of medical visit, mechanical ventilation [yes/no], respiratory diagnostic procedures [yes/no], IV fluids [yes/no], selected respiratory medications [yes/no], antibiotic use [yes/no]), the number, percent, odds ratios, and associated two-sided 95% CI will be presented.

- For continuous variables (the number of medical visits, length of hospital stay, total number of mechanical ventilation episodes, total number of hours/days on mechanical ventilation, total number of prescriptions, total number of antibiotic use days), the mean, SD, difference in means, and associated 2-sided 95% CI will be presented.

6.3.1.11.2. Supplementary Analysis

Some healthcare utilization variables will also be compared between RSVpreF and placebo groups using only RSV-positive MA-LRTI cases.

6.3.1.12. IgG Concentrations Against Prefusion F Measured at Birth

- Analysis set: Evaluable immunogenicity – infant (Section 4).

- Analysis methodology: Descriptive summary statistics. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.

- GMCs of the IgG against prefusion F subgroup A and subgroup B, and combined RSV A/B, at birth will be presented. For each vaccine group, n, GMC, and 95% CI will be presented.

6.3.1.13. MA-RTI, MA-LRTI, and Severe MA-LRTI Due to RSV Occurring 0 to 730 Days After Birth in Premature Infants <37 Weeks of Age

- Analysis set: Evaluable efficacy – infant (Section 4).

- Analysis methodology: VE will be analyzed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. Results obtained after the infant received palivizumab or another monoclonal antibody targeting RSV or after he/she had transfusions of more than 20 mL/kg of any blood products at ≤180 days of age will be excluded.

- For each group, the number (n), percentage, and 95% CI of MA-RTI, MA-LRTI and severe MA-LRTI due to RSV cases occurring within 0 to 730 days after birth will be presented for each group.

- VE compared to placebo along with the 95% CI will be presented for each analysis interval separately.

6.3.2. Exploratory Endpoints: Maternal Participants

6.3.2.1. Incidence of All-Cause MA-RTIs From Vaccination Up to 180 Days After Delivery

- Analysis set: Safety – maternal (Section 4).
- Analysis methodology: Descriptive summary statistics for all-cause MA-RTI up to 180 days.
- For each group, the number (n), percentage, and 95% CI of MA-RTI all-cause cases occurring up to 180 days will be presented.

6.3.2.2. RSV A and RSV B Serum Neutralizing Titers Measured Before Vaccination and at Delivery Visit

6.3.2.2.1. Main Analysis

- Analysis set: Evaluable immunogenicity maternal (Section 4).
- Analysis methodology: Descriptive summary statistics. Results obtained from out-of-window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.
- GMTs of the RSV A and RSV B serum neutralizing titers at each available time point will be descriptively summarized for each vaccine group, along with associated 2-sided 95% CIs.
- GMT of the combined RSV A/B serum neutralizing titer 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 serum neutralizing titers from before vaccination to each available time point after vaccination for each vaccine group.
- GMFR and associated 2-sided 95% CIs will be provided for the combined RSV A/B serum neutralizing 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 serum neutralizing titers at each available time point after vaccination will be calculated, along with associated 2-sided 95% CIs.
- GMR of the RSV vaccine group to the placebo group for the combined RSV A/B serum neutralizing titer at each available time point after vaccination will be calculated, along with associated 2-sided 95% CIs.

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

6.3.2.2.2. Sensitivity Analysis

A sensitivity analysis will be performed to exclude immunogenicity data (RSV-neutralizing titers and IgG against prefusion F) from mothers following onset of RSV infection between vaccination and delivery (based on evidence from the nonvaccine-antigen assay).

6.3.2.2.3. Supplementary Analysis

The main analysis will also be performed based on the mITT immunogenicity maternal population. This analysis will be performed if there is at least 10% difference between the evaluable immunogenicity maternal population and mITT immunogenicity maternal population.

6.3.2.3. IgG Concentrations Against Prefusion F Measured Before Vaccination and at Delivery Visit

- Analysis set: Evaluable immunogenicity maternal (Section 4).

- Analysis methodology: Descriptive summary statistics. Results obtained from out -of -window blood draws will also be removed. Missing serology results will not be imputed, as MCAR is assumed.

- GMCs of IgG against prefusion F at each available time point by vaccine group. For each vaccine group, n, GMC, and 95% CI will be presented.

- GMFRs and associated 2-sided 95% CIs will be provided for IgG concentrations against prefusion F from before vaccination to each available time point after vaccination for each vaccine group.

6.3.2.4. Ig Concentrations Against Nonvaccine RSV Antigens Measured Before Vaccination and at Delivery Visit

All attributes (including analysis methodology and reporting results) for this endpoint will be similar to those stated in Section 6.3.2.3.

6.4. Subset Analyses

Table 10 summarizes the defined subgroup analyses. Additional subset analyses (not defined here) may also be performed if deemed necessary. Immunogenicity testing may be performed on subsets of participants if needed prior to testing on all study participants and may be reported separately.

Table 10. Subgroup Analysis for Infant Participants

Subgroup	Endpoints	Population
GA at the time of vaccination (≥24 to <28 weeks, ≥28 to <32 weeks, ≥32 to ≤36 weeks)	• Primary efficacy endpoints • Immunogenicity endpoints • Hospitalization due to RSV (up to 730 days)	• Evaluable efficacy – infant • Evaluable immunogenicity – infant • Evaluable efficacy – infant
Time from vaccination to delivery		
≤14 Days >14 Days and ≤30 days >30 Days	• Immunogenicity endpoints	• mITT immunogenicity – maternal/infant
Country	• Primary efficacy endpoints • Immunogenicity endpoints • Pregnancy & birth outcome • Hospitalization due to RSV (up to 730 days)	• Evaluable efficacy – infant • Evaluable immunogenicity – infant • Safety – maternal/infant • Evaluable efficacy – infant
Country subcategories (level of income)[4]	• Primary efficacy endpoints • Immunogenicity endpoints • Pregnancy & birth outcome • Hospitalization due to RSV (up to 730 days)	• Evaluable efficacy – infant • Evaluable immunogenicity – infant • Safety – maternal/infant • Evaluable efficacy – infant
Demographic risk factors		
Breastfeeding (exclusivity and duration)	• Primary and secondary efficacy endpoints	• Evaluable efficacy – infant
Maternal smoking (smoker [current]/nonsmoker)	• Primary and secondary efficacy endpoints	• Evaluable efficacy – infant
Number of household members	• Primary and secondary efficacy endpoints	• Evaluable efficacy – infant
Infants who received palivizumab (yes/no)	• Primary and secondary efficacy endpoints	• mITT efficacy – infant
Duration of planned follow-up (12 or 24 months)	• Demographics	• Safety – infant
Age at vaccination: <18 years/≥18 years	• Safety endpoints • Immunogenicity endpoints • Primary and secondary efficacy endpoints	• Safety – maternal/infant • Evaluable immunogenicity – maternal/infant • Evaluable efficacy – infant
Gender	• Safety endpoints	• Safety – infant
Race	• Safety endpoints	• Safety – maternal/infant

Abbreviation: GA = gestational age; RSV = respiratory syncytial virus.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Baseline Summaries for Maternal Participants

For each group, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity; in addition, GA at vaccination will be presented for the following groups: ≥24 and <28 weeks, ≥28 to <32 weeks, and ≥32 to ≤36 weeks, and >36 weeks), current/former substance use, and obstetric history as described in Section 3.5.4 will be generated for each group based on the maternal safety population.

The number and proportion of participants with at least 1 medical history PT, arranged by SOC, will be tabulated for each group. The medical history summary is based on the maternal 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 infant 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 delivery visit, those who withdrew before delivery, along with the reasons for withdrawal, those 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. Information regarding additional informed consent from a legally authorized representative if a mother cannot provide informed consent, will be listed. This will be created only for infants.

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

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

The numbers and percentage 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.

Data listings for participants who withdrew during the study will be generated. In addition, data listings for participants excluded from different populations will be generated separately. These listings will be generated separately for maternal and infant participants.

The important protocol deviations listings will be generated separately for maternal and infant participants.

6.5.3. Concomitant Medications and Nondrug Treatments

Nonstudy vaccines and medications taken during pregnancy or during the study will be categorized according to the WHO Drug Dictionary and summarized in accordance with the sponsor reporting standards. These will be generated (if needed) separately for maternal and infant participants.

MA-RTI concomitant medications and antibiotic medications associated with an MA-RTI event may be summarized separately (antibiotics will be identified based on ATC4 category in the database and confirmed by Pfizer clinical personnel on an ongoing basis). These summaries will be generated separately for maternal and infant participants.

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. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis. 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 6.1.2 and Section 6.1.3.

In addition, another summary will be created to present AEs of special interest (as defined in the protocol and SAP).

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. Listings of medical device related AEs will be generated only for maternal participants.

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 6.1.3.1 and Section 6.1.3.2.

A descriptive summary of severity of the assessment collected prior to vaccination on Day 1 (baseline assessment) for the prespecified systemic events will be presented by vaccine group.

In addition, participant data listings will be provided for all reactogenicity data (separate for local reactions and systemic events) as well as a listing for participants experiencing severe redness or swelling.

6.6.3. Physical Examination, Including Vital Signs

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

6.6.4. Obstetric Examinations and Pregnancy Outcomes

Descriptive summaries and data listings will be generated for the obstetric examination findings and pregnancy outcomes. The incidence of maternal pregnancy outcomes including (but not limited to) location of the delivery, mode of delivery, eg, cesarean delivery (with subsets of elective, semielective, and emergency) vs vaginal delivery (with a subset of "operative vaginal delivery" as characterized by the use of "forceps" or "vacuum"), and complications experienced during delivery will be presented. The summaries and listings for these data will be generated only for maternal participants.

6.6.5. Birth Outcomes

Descriptive summaries and data listings will be generated for the birth outcomes. The summaries and listings for these data will be generated only for infant participants. In addition to the information collected in the CRF, the following groups will also be presented for the GA at birth: ≥24 and <28 weeks, ≥28 to <34 weeks, ≥34 to <37 weeks, ≥37 to <42 weeks, and ≥42 weeks.

6.6.6. Specific RTI Diagnoses

A descriptive summary and data listing will be generated for specific RTI diagnoses (identified by Pfizer clinical personnel on an ongoing basis). The summary and listing for these data will be generated only for infant participants using the AE page (NDCMC) and the illness details page.

7. INTERIM ANALYSES

7.1. Introduction

An interim analysis may be performed to assess efficacy and safety after at least 50% of the planned number of cases of MA-LRTI due to RSV (as determined by the EAC) have occurred. Interim analysis results may be used for internal business decisions regarding future study planning, stopping for futility, or stopping for early success.

This study will use an E-DMC. Refer to the E-DMC charter for further details.

7.2. Interim Analyses and Summaries

Interim analyses may be performed to assess efficacy and safety after at least 43 cases of MA-LRTI-due-to-RSV within 90 days have occurred.

Based on the fraction of cases included in an interim analysis, an alpha level will be derived based on a Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. For example, a first interim analysis at 43 cases would use a 1-sided significance level of 0.014%. If a second interim analysis were performed, for example at 62 cases, it would use a 1-sided significance level of 0.15%. The final analysis at the target number of cases would use a 1-sided significance level of 2.45%. Implementation of these 1-sided significance levels ensures that the overall type I error for the primary endpoint will be no more than 0.025. The alpha levels used at interim and final analyses will depend on the exact fraction of cases available at the interim analysis. The exact number of cases at each interim analysis is not fixed and may be decided based on operational reasons. However, no fewer than 43 cases will be included in the first interim analysis and no fewer than 62 cases will be included in the second interim analysis.

The order of cases included in the interim analysis will be determined by the EAC as those first confirmed to meet the protocol-defined criteria. When the target number of cases for an interim analysis is reached, it is possible that additional potential cases will be under adjudication. Only cases that have been fully adjudicated up to the day of data snapshot will be included in an interim analysis.

Consideration will be given to stopping the study for efficacy if the analysis of either primary endpoint through 90 days indicates statistically significant efficacy. Secondary endpoints will not be tested at the interim analysis.

Use of (2-sided) alpha across primary and secondary endpoints after a successful interim analysis will be as follows: for the endpoints inspected at the interim analysis (MA-LRTI and severe MA-LRTI at 90 days), the O'Brien-Fleming alpha spending function determines the alpha to be used and will be split between the endpoints using the Bonferroni correction. Since MA-LRTI through 180 days was inspected at the first interim analysis in April 2022 with a 2-sided alpha of 0.0017, the analysis of the primary endpoints at 120 days and later after a successful interim analysis will use a 2-sided alpha of 0.05 - 0.0017 = 0.0483, to be split between the endpoints using the Bonferroni correction. If the hypothesis for both the primary endpoints is successful through 180 days, the 3 secondary endpoints will be analyzed

using alpha = 0.05/3 assigned to each; and if the hypothesis for 1 primary endpoint is not successful through 180 days, the 3 secondary endpoints will be analyzed using alpha = 0.025/3 assigned to each.

Futility will also be assessed at the interim analyses using conditional power. Specifically, the probability of the MA-LRTI endpoint analysis being successful at the final analysis, given the interim data, will be calculated, assuming that the design assumption of 60% efficacy applies to future data. Conditional power will be calculated by the exact binomial method, consistent with the primary analysis method. This calculation is only possible for the MA-LRTI primary endpoint since there is no explicit case target for the severe MA-LRTI endpoint. Consideration will be given to stopping the study for futility if the conditional power falls below 20%; however, other levels of conditional power may trigger a futility decision based on business considerations. Changes from the 20% level will be documented in a DMC charter update.

For example, if there were 2 interim analyses after 43 and 62 cases, Table 11 indicates case splits for which stopping the study will be considered.

Table 11. Example of Estimated Vaccine Efficacy and Confidence Intervals at an Interim Analysis

Total Cases	RSV Vaccine Group Cases	Placebo Group Cases	VE (CI)[a]	Notes
43 (First interim)	24	19	-26% (-145%, 34%)	Conditional power <20%,[b] possible futility declaration
43 (First interim)	6	37	84% (27%, 98%)	Maximum number of vaccine group cases permitted to declare VE >20%
62 (Second interim)	29	33	12% (-49%, 49%)	Conditional power <20%,[b] possible futility declaration
62 (Second interim)	14	48	71% (25%, 91%)	Maximum number of vaccine group cases permitted to declare VE >20%

Abbreviation: VE = vaccine efficacy.

a. Confidence level for efficacy declaration based on half the available alpha at each interim, assuming both MA-LRTI and severe MA-LRTI endpoints were inspected; 95% confidence level for futility.

b. Other conditional power levels may be considered as a trigger for a futility decision.

8. REFERENCES

1. Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. Commun Stat Theory Methods. 1988;27(6)1305-22.

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

3. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

4. The World Bank Group. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed: 19 May 2021.

9. APPENDICES

Appendix 1. Specific Birth Outcomes

The specific birth outcomes of interest for this study are listed below:

- AEs categorized as AESIs in the database
- Neonatal death
- Congenital malformations/anomalies
- Other neonatal problems
- Final Apgar score (at either 1, 5, or 10 minutes) less than 7

Appendix 2. List of Abbreviations

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
Apgar	appearance, pulse, grimace, activity, and respiration
ATC4	Anatomic Therapeutic Chemical classification, Level 4
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CRF	case report form
DMC	data monitoring committee
EAC	event adjudication committee
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
ICU	intensive care unit
Ig	immunoglobulin
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IV	intravenous
IRT	interactive response technology
LLOQ	lower limit of quantitation
LRTI	lower respiratory tract illness
MA-LRTI	medically attended lower respiratory tract illness
MA-RTI	medically attended respiratory tract illness
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
NDCMC	newly diagnosed chronic medical condition
PA	protocol amendment
PCR	polymerase chain reaction
PT	preferred term
QNS	quantity not sufficient
RAD	reactive airway disease
RCDC	reverse cumulative distribution curve
RR	relative risk
RSV	respiratory syncytial virus

Appendix 2. List of Abbreviations

Abbreviation	Term
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RTI	respiratory tract illness
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	system organ class
ULOQ	upper limit of quantitation
VE	vaccine efficacy
VRD	Vaccine Research & Development
WHO	World Health Organization

Document Approval Record

Document Name:	C3671008 Statistical Analysis Plan V6 Clean Copy, 02Sep2022
Document Title:	A PHASE 3, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN INFANTS BORN TO WOMEN VACCINATED DURING PREGNANCY

Signed By:	Date(GMT)	Signing Capacity
PPD	02-Sep-2022 15:28:26	Final Approval