Protocol

Protocol for: Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023;388:1451-64. DOI: 10.1056/NEJMoa2216480

This trial protocol has been provided by the authors to give readers additional information about the work.

Bivalent RSVpreF Vaccine in Pregnancy to Prevent RSV Illness in Infants

This supplement contains the following items:

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Final statistical analysis plan (version 6) that is the original statistical analysis plan and all cumulative amendments (shown on page 375)……..Page 368



A PHASE 3, RANDOMIZED, DOUBLE- OR OBSERVER-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

Investigational Product Number:	PF-06928316
Investigational Product Name:	Respiratory Syncytial Virus (RSV) Vaccine
United States (US) Investigational New Drug (IND) Number:	017931
European Clinical Trials Database (EudraCT) Number:	2019-002943-85
Protocol Number:	C3671008
Phase:	3

Short Title: A Phase 3 Trial to Evaluate the Efficacy and Safety of RSVpreF in Infants Born to Women Vaccinated During Pregnancy.

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Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	05 December 2019	Not applicable (N/A)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Indication

Pfizer's respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF) is a prophylactic vaccine that is being investigated for the prevention of medically attended RSV-associated lower respiratory tract illness (LRTI) in infants by active immunization of pregnant women.

Rationale

There is a large unmet medical need that could be addressed by an effective RSV prophylaxis in infancy. Given the global burden of disease, maternal immunization offers an attractive strategy for infant disease prevention. Both preclinical studies in animals and interim data from a Phase 1/2 study in healthy nonpregnant adults have demonstrated acceptable tolerability and safety of RSVpreF. A robust immune response has also been observed in participants from the aforementioned trial. RSVpreF is currently under assessment in healthy pregnant women 18 through 49 years of age (Study C3671003: *A Phase 2b, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants; ClinicalTrials.gov identifier: NCT 04032093*).

This randomized, double- or observer-blinded, placebo-controlled Phase 3 study is designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended lower respiratory tract illness (MA-LRTI) in infants.

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Objectives, Estimands, and Endpoints

Infant Participants

Primary Efficacy Objectives – Infant Participants	Estimands	Primary Efficacy Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	Vaccine efficacy (VE), defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI as confirmed by the endpoint adjudication committee (EAC): • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

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Primary Safety Objective – Infant Participants	Estimand	Primary Safety Endpoints – Infant Participants
To describe the safety of RSVpreF.	• In infant participants born to maternal participants receiving 1 dose of investigational product, the percentage of participants with each safety endpoint in each vaccine group.	• Specific birth outcomes. • Adverse events (AEs) from birth to 1 month of age. • Serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs): o from birth through 6 months of age (*first RSV season for all infant participants*). o from birth through 12 months of age (*for all infant participants*). o from birth through 24 months of age (*for infant participants born to maternal participants enrolled during the first year of the study*).
Secondary Efficacy Objectives – Infant Participants	**Estimands**	**Secondary Efficacy Endpoints – Infant Participants**
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Hospitalization due to RSV: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	MA-LRTI due to any cause with protocol-defined criteria: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

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Exploratory Objectives – Infant Participants	Estimands	Exploratory Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of medically attended respiratory tract illness (MA-RTI) due to RSV.		RSV-positive MA-RTI as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth. • occurring within 150 days after birth. • occurring within 180 days after birth. • occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.		Hospitalization due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV in infants older than 6 months of age.		Severe MA-LRTIs due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.		MA-LRTIs due to any cause occurring 181 to 730 days after birth.
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.		RSV subgroup A– and subgroup B–specific MA-LRTI as confirmed by the EAC occurring within 181 days after birth.
To describe the non-RSV infectious etiology of MA-RTI in the study population.		Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits occurring within 181 days after birth.
To evaluate RSV-neutralizing antibody titers elicited by RSVpreF and transferred transplacentally.		RSV A– and RSV B–neutralizing antibody titers measured at birth.
To assess the impact of RSVpreF on RSV illness based on socioeconomic factors.		Primary and secondary efficacy by select demographic risk factors (eg, breastfeeding, maternal smoking, number of household members).

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To assess the effect of RSVpreF on healthcare utilization.		Mean/median composite score summarizing healthcare utilization, 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 intravenous (IV) fluids, requirement for prescriptions, and antibiotic use.

Maternal Participants

Primary Safety Objective – Maternal Participants	Estimand	Primary Safety Endpoints – Maternal Participants
To describe the safety and tolerability of RSVpreF.	In maternal participants receiving 1 dose of investigational product, the percentage of maternal participants with each safety endpoint in each vaccine group.	The incidence of: • 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 (*Visit 1 through the 6-month-postdelivery study visit*).
Exploratory Objectives – Maternal Participants	**Estimands**	**Exploratory Endpoints – Maternal Participants**
To describe MA-RTI in this study population.		The incidence of all-cause MA-RTIs from vaccination up to 180 days after delivery.
To evaluate the immune responses elicited by RSVpreF.		• RSV A– and RSV B–neutralizing antibody titers and preF immunoglobulin G (IgG) titers measured: • before vaccination. • at delivery.

Overall Design

This is a Phase 3, multicenter, randomized, double- or observed-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, as well as 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.

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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 the statistical analysis section (Section 9.2). There is no specific case target for the additional primary endpoint of severe MA-LRTI. The total enrollment number of maternal participants may vary depending on the incidence rate of the primary endpoint in the infant participants, the true underlying VE, and a potential early stop for efficacy or futility. In the event that efficacy in the infant population is demonstrated at the interim analysis, enrollment of maternal participants may continue in order to obtain safety evaluations in an adequate number of maternal and infant participants to support vaccine registration with national health authorities.

Based on these considerations, and in order to accumulate endpoint cases, 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 is anticipated that approximately 6900 mother-infant pairs may be needed to accumulate 124 per-protocol cases.

Study-eligible pregnant women will be randomized in a 1:1 ratio to receive RSVpreF or placebo. For the RSV vaccine group, a single dose and formulation of RSVpreF will be selected based on data from the maternal C3671003 study (*ClinicalTrials.gov identifier: NCT 04032093*). The selected dose of RSV prefusion F antigen in RSVpreF will be 120 µg (60 µg A and 60 µg B) or 240 µg (120 µg A and 120 µg B). The selected formulation will be with or without aluminum hydroxide ($Al[OH]_3$).

Once they have provided informed consent, the women will be referred to as "maternal participants" and will be followed from vaccination during pregnancy until 6 months after delivery. Assessments will include parameters to allow descriptions of safety, tolerability, and immunogenicity of the vaccine in maternal participants.

Infants born to women who receive RSVpreF or placebo in their second or third trimester will be referred to as "infant participants." Infant participants born to women enrolled during the first year of the study will have 6 scheduled study visits during their 24 months of participation, whereas all other infant participants will have up to 4 scheduled study visits during their proposed 12 months of participation. 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. For infant participants enrolled during the first year of the study, the extended 12-month study duration will involve longer-term respiratory tract illness (RTI) surveillance and safety oversight to address safety and the possibility of conferred enhanced protection (antibody persistence) during a second RSV season.

All MA-RTIs meeting the protocol definition for a potential study endpoint will be adjudicated by an independent adjudication committee.

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Planned Duration

Pregnant women will participate in the study from enrollment during their pregnancy, and for approximately 6 months after delivery of their infants. The total duration will be up to approximately 10 months, depending on gestational age (GA) at the time of vaccination and when the infant is actually born.

All eligible infant participants born to enrolled maternal participants during the first year of the study will participate in the study from the time of birth and will be followed for up to 24 months for RSV surveillance and safety for the secondary and exploratory endpoints of the study. All other infants will participate from the time of birth and for at least 12 months after birth.

Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC) to monitor vaccine safety and efficacy and study futility.

Statistical Methods

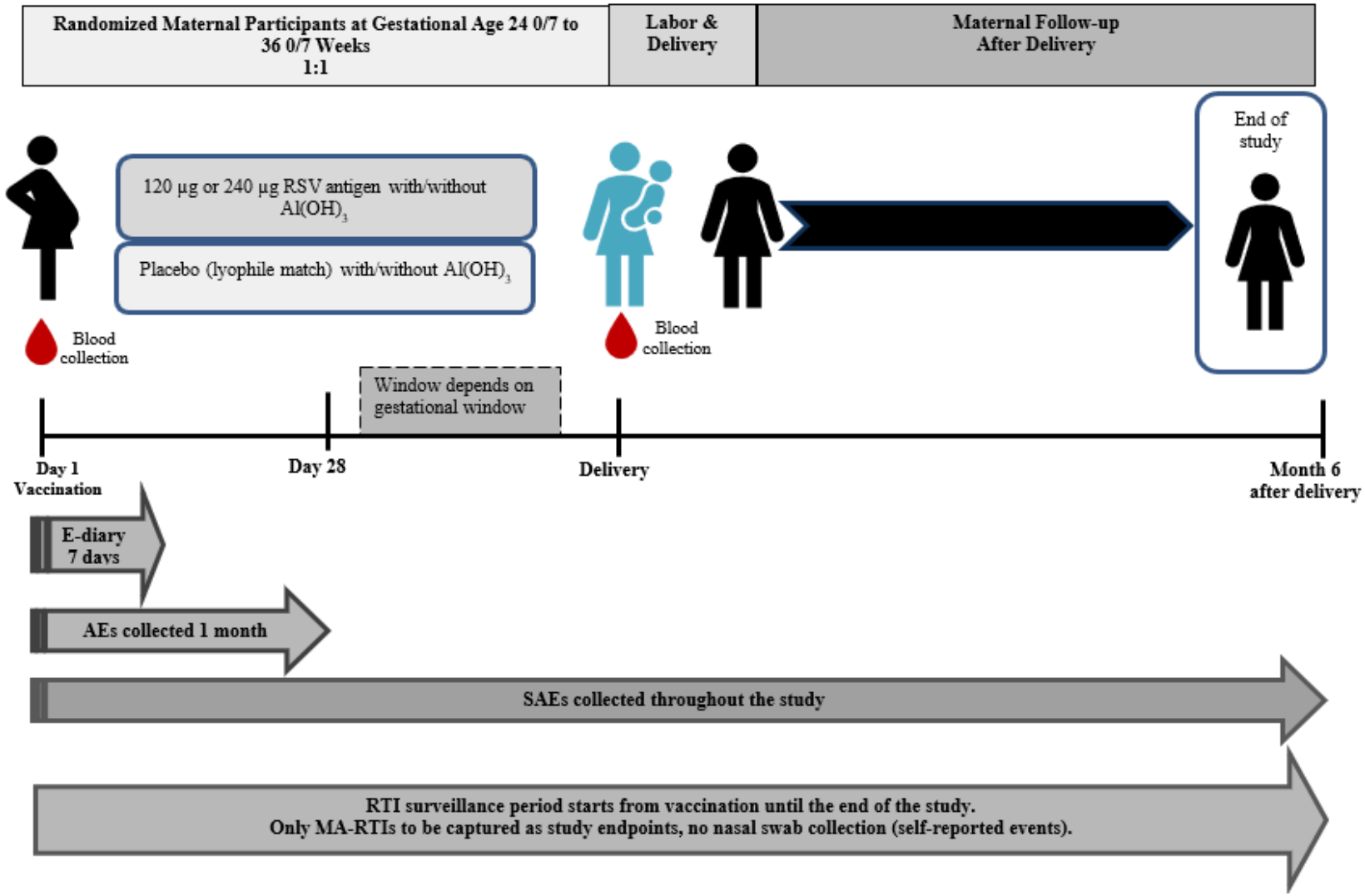
The primary hypothesis to be tested is that VE with respect to MA-LRTI due to RSV or severe MA-LRTI due to RSV in infants within at least 90 days after birth is more than 20%, relative to placebo. The 2 primary endpoints will be tested in parallel using a Hochberg multiplicity adjustment procedure. VE will be estimated using the exact conditional binomial method. There will also be hierarchical testing of the primary endpoints to 120 days, 150 days, and 180 days, conditional on success of the analysis for the shorter intervals. A single interim analysis of the primary endpoint with the opportunity to stop the study for efficacy or futility may be included. At the end of the trial, the RSV vaccine may be deemed efficacious if there are 43 or fewer cases of MA-LRTI due to RSV in the RSV vaccine group out of the 124 total primary-endpoint cases. This corresponds to estimated VE = 47% with 95.1% confidence interval (CI) = (22%, 64%). For severe MA-LRTI, assuming a total of 50 cases occur, the vaccine may be deemed efficacious if there are 14 or fewer cases in the RSV vaccine group. This corresponds to estimated VE = 61% with 95.1% CI = (26%, 81%).

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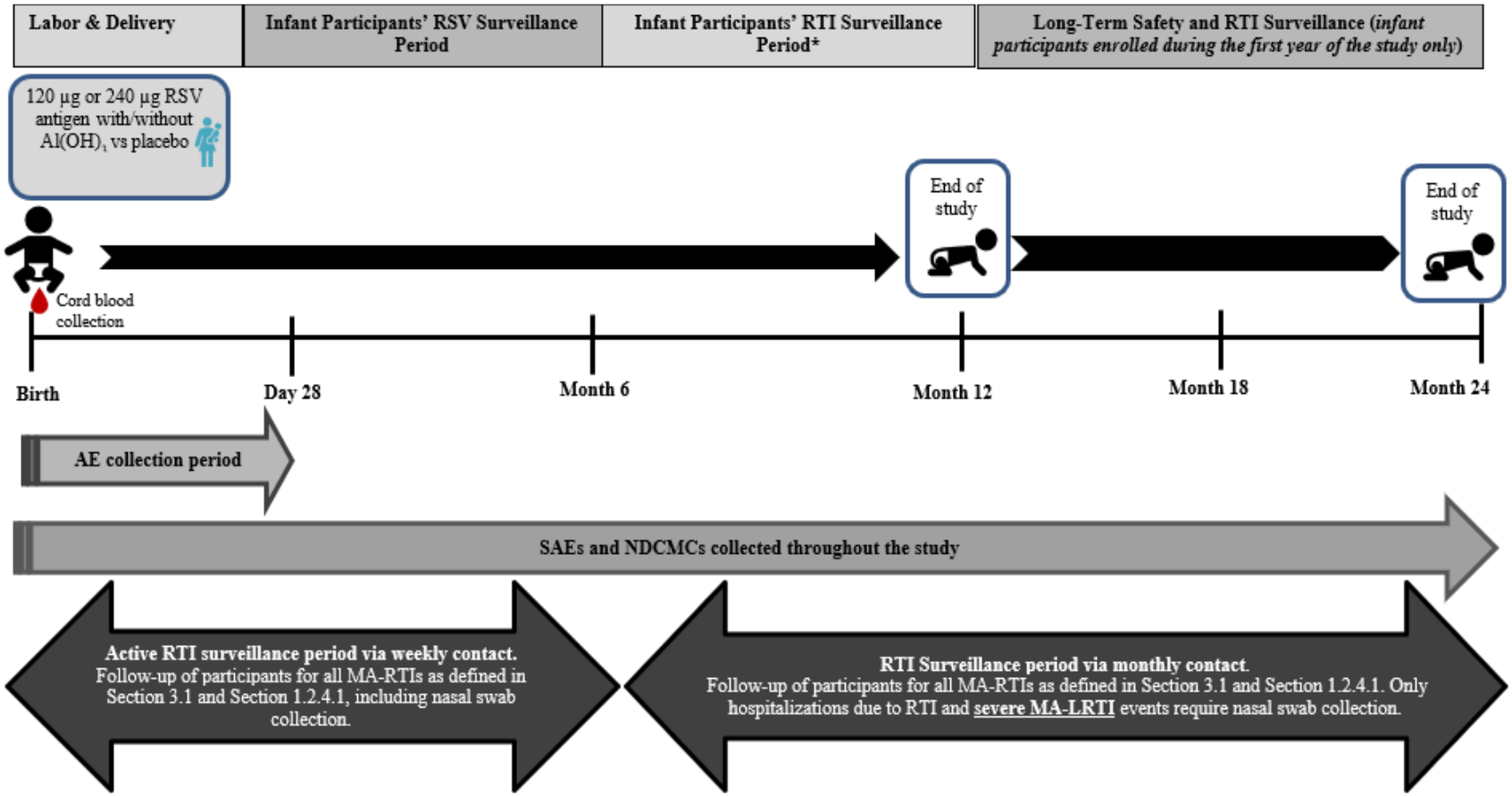
1.2. Schematic for Study Participants

1.2.1. Study Design – Maternal Participants



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1.2.2. Study Design – Infant Participants



*Study completion for all infant participants will be up to Month 12, except for infant participants enrolled during the first year of the study, which will be up to Month 24.

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Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.2.3. Schedule of Activities for Maternal Participants

Visit Description	Screening and Vaccination[a]	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	**Day -28 to Day 1**	**28 to 42 Days After Vaccination**		**180 to 210 Days After Delivery**
Type of Visit	**Clinic**	**Clinic or Telephone**	**Maternity Unit**	**Clinic or Telephone**
Informed consent for maternal participant and her infant	X			
Assign single maternal participant identifier	X			
Demography	X			
Medical history including obstetric history[d]	X			
Record current alcohol, tobacco, marijuana, or any illicit drug usage	X			
Targeted physical examination including vital signs	X			
Record details of any antenatal and/or postnatal steroid treatment, monoclonal antibodies, blood products, or Rho(D) immune globulin	X	X	X	X
Record details of intrapartum antibiotic prophylaxis (IAP) for maternal group B streptococcal colonization			X	
Record nonstudy vaccine information	X	X	X	X
Review eligibility criteria	X	X	X	
Review temporary delay criteria	X			
Blood draw for serologic assessment (~15 mL)	X		X	
Assign randomization and container number	X			
E-diary training, dispense digital thermometer and measuring device[e]	X			
Obtain and record baseline assessment of prespecified systemic events prior to vaccination in the e-diary				
Administer investigational product	X			
Postvaccination observation (at least 30 minutes) and assessment of immediate adverse events	X			
Record pregnancy outcome information			X	

Visit Description	Screening and Vaccination[a]	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	Day -28 to Day 1	28 to 42 Days After Vaccination		180 to 210 Days After Delivery
Type of Visit	Clinic	Clinic or Telephone	Maternity Unit	Clinic or Telephone
Review e-diary data[f]	X----------			
Record adverse events, as appropriate[g]	X----------			
Record serious adverse events, as appropriate[g]	X	X	X	X
Record details pertaining to MA-RTI visit[h]	Assessment of confirmed MA-RTI events during the study as detailed in Section 1.2.3.1 of the schedule of activities			

Abbreviations: e-diary = electronic diary; IAP = intrapartum antibiotic prophylaxis; MA-RTI = medically attended respiratory tract illness.

a. In countries/locales where certain prenatal assessments are not routinely performed, prerandomization assessments and test results to confirm maternal participant eligibility for this clinical trial can be obtained and reviewed by the investigator or qualified designee up to 28 days prior to vaccination.
b. The 1-month follow-up visit will not be performed if delivery occurs before this visit. Active elicitation and collection of AEs and SAEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination. Once delivery occurs, the visit windows are calculated based on the delivery date.
c. The delivery visit includes the time from when a participant is admitted into labor through discharge following delivery of her infant. Please see Section 8.10.3 for required protocol assessments at this visit.
d. Where an obstetric ultrasound examination is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination. As part of the obstetric history, details regarding the last menstrual period (LMP) and estimated delivery date (EDD) are to be recorded.
e. Maternal participants will be issued a measuring device to measure local reactions and a digital thermometer for recording daily temperatures, and will be provided with instructions on their use. Maternal participants and or the field worker (as per local practice) will record (in an e-diary) a baseline assessment of prespecified systemic events prior to vaccination and reactogenicity events from Day 1 to Day 7 following vaccination (where Day 1 is the day of vaccination). Remind maternal participants that the study staff/field worker may contact them to obtain additional information on events entered into the e-diary. Ask maternal participants to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination, to determine if an unscheduled reactogenicity visit is required. Based on local rules of practice, the maternal participant may be referred to the appropriate healthcare facility at the discretion of a field worker if there are any concerns.
f. Site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate maternal participant compliance and as part of the ongoing safety review.
g. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs and SAEs through 28 days after vaccination. From 28 days after vaccination until the maternal participant completes the study, all SAEs will be collected. Please see Section 8.3.1 for reporting requirements and timelines.
h. A confirmed MA-RTI is defined as an expected RTI event based on the assessments detailed in the schedule of assessments in Section 1.2.3.1. These events will not be captured as safety events, unless the investigator or an appropriate designee deems them to be related to the investigational product.

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1.2.3.1. Schedule of Activities for Maternal Participants: RTI Surveillance for Medically Attended Respiratory Tract Illness Visits (Vaccination Until the End-of-Study Visit)

Visit Description	Assessments of MA-RTI[a]
Visit Window	**As Soon as Possible After Confirmed MA-RTI**
Type of Visit	**Telephone**
Record details of a confirmed MA-RTI	X
Details of an acute illness visit AND a report of 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	X
Obtain standard-of-care records, including local NAAT testing results (if applicable)[b]	X
Record nonstudy vaccine information	X
Record AEs and SAEs, as appropriate[c]	X
Complete the CRF with details	X

Abbreviations: CRF = case report form; MA-RTI = medically attended respiratory tract illness; NAAT = nucleic acid amplification technology; RSV = respiratory syncytial virus; RTI = respiratory tract illness.

a. Confirmed cases of MA-RTI will be collected from vaccination until the maternal participant completes the study. The assessment of the event would involve a telephone call, or a clinic visit if determined by the investigator to be warranted.
b. Site staff will review and collect data pertaining to the illness, including location of infection (upper or lower RTI) and any local NAAT testing results (RSV, influenza, etc), if available.
c. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs and SAEs through 28 days after vaccination. From 28 days after vaccination until the maternal participant completes the study, all SAEs will be collected. Please see Section 8.3.1 for reporting requirements and timelines.

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1.2.4. Schedule of Activities for Infant Participants

Participants	All Infant Participants				Long-Term Follow-up for Infant Participants Enrolled in the First Year of the Study[a]	
Visit Number	1	2	3	4	5	6
Visit Description	Birth	1-Month Follow-up	6-Month Follow-up	12-Month Follow-up	18-Month Follow-up	24-Month Follow-up
Visit Window (Days)	Birth to 7 Days After Birth	28 to 48 Days After Birth	180 to 210 Days After Birth	350 to 378 Days After Birth	525 to 574 Days After Birth	714 to 742 Days After Birth
Type of Visit	Hospital	Clinic	Clinic	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone
Assign infant participant identifier	X					
Demography	X					
Collect background factors[b]	X	X	X	X	X	X
Collect birth outcome information including infant's birth data and appearance, pulse, grimace, activity, and respiration (Apgar) score	X					
Obtain and record infant's length, head circumference, and weight	X	X	X	X (if clinic visit)		X (if clinic visit)
Physical examination including vital signs	X					
Targeted physical examination including vital signs		X	X	X (if clinic visit)		X (if clinic visit)
Record immune globulin, monoclonal antibodies (eg, Synagis), or blood products (eg, whole blood, packed cells)	X	X	X	X	X	X
Review eligibility	X					
Cord blood sample (~10 mL) for serologic assessment[c]	X					
Record adverse events, NDCMCs, and serious adverse events, as appropriate[d]	X	X	X	X	X	X

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Participants	All Infant Participants				Long-Term Follow-up for Infant Participants Enrolled in the First Year of the Study[a]	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Visit Description	**Birth**	**1-Month Follow-up**	**6-Month Follow-up**	**12-Month Follow-up**	**18-Month Follow-up**	**24-Month Follow-up**
Visit Window (Days)	**Birth to 7 Days After Birth**	**28 to 48 Days After Birth**	**180 to 210 Days After Birth**	**350 to 378 Days After Birth**	**525 to 574 Days After Birth**	**714 to 742 Days After Birth**
Type of Visit	**Hospital**	**Clinic**	**Clinic**	**Clinic or Telephone**	**Clinic or Telephone**	**Clinic or Telephone**
Surveillance reminder contact	Contact with the infant participants' parent(s) or legal guardian(s) approximately every week until Visit 3		From Visit 3, contact with the infant participant's parent(s) or legal guardian(s), approximately every 28 to 35 days until the end of the study			
Assessment of MA-RTIs[e]	Assessment of MA-RTI events during the active RSV surveillance period as detailed in Section 1.2.4.1 of the schedule of activities		Assessment of MA-RTI events as detailed in Section 1.2.4.1 of the schedule of activities			

Abbreviations: MA-RTI = medically attended respiratory tract illness; NDCMC = newly diagnosed chronic medical condition; RSV = respiratory syncytial virus.

a. Applicable only for infant participants enrolled during the first year of the study.
b. Background factors as detailed in Appendix 5 related to socioeconomic and health factors that may impact the incidence of RSV illness.
c. Cord blood must be obtained on the day of birth. Cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been clamped and cut. If cord blood is unavailable, a blood sample may be collected from the infant participant preferably within the first 24 hours but up to 7 days after birth. The infant's weight must be used to determine the volume of blood that can be collected.
d. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs, NDCMCs, and SAEs through 28 days after birth. From 29 days after birth until the infant participant completes the study, NDCMCs and SAEs will be collected. 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 (eg, asthma).
e. A confirmed MA-RTI is defined as an expected study event based on the assessments detailed in the schedule of assessment in Section 1.2.4.1. These events will not be captured as safety events, unless the investigator or an appropriate designee deems them to be related to the investigational product.

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1.2.4.1. Schedule of Activities for Infant Participants: Medically Attended Respiratory Tract Illness Assessment Visits During the Study

Visit Description	MA-RTI Assessments During the Active RSV Surveillance Period[a]	MA-RTI Assessments[b]
Assessment Period During the Study	**Birth to 180 Days After Birth**	**181 Days After Birth to the End of the Study**
Visit Window (Days)	**As Soon as Possible After Confirmed MA-RTI and Within 72 Hours**	**As Soon as Possible After Confirmed MA-RTI and Within 72 Hours**
Type of Visit	**Hospital, Home, or Clinic**	**Hospital, Home, Clinic, or Telephone**
Surveillance reminder contact	Contact the infant participants' parent(s) or legal guardian(s) approximately every week until Visit 3	From Visit 3, contact the infant participants' parent(s) or legal guardian(s), approximately every 28 -35 days until the end of the study
Record confirmed MA-RTI as detailed in Appendix 6, as appropriate	X	X
Record details of the RTI, including 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	X	X
In the event that the MA-RTI involved hospitalization, assess the details of hospitalizations due to RTI and assess whether the event meets the definition of a severe MA-LRTI[c]		X
Perform an in-person study visit and record vital signs and targeted physical examination results (heart rate, respiratory rate, SpO_2, chest wall indrawing)	X	X (for *hospitalized RTIs or severe MA-LRTIs only*)
Record local NAAT testing results, if performed and available[d]	X	X
Collect nasal swab (for RT-PCR)[e]	X	X (for *hospitalized RTIs or severe MA-LRTIs only*)
Collect background factors associated with MA-RTI[f]	X	X
Record immune globulins, monoclonal antibodies (eg, Synagis) or blood products (eg, whole blood, packed cells)	X	X

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Visit Description	MA-RTI Assessments During the Active RSV Surveillance Period[a]	MA-RTI Assessments[b]
Assessment Period During the Study	**Birth to 180 Days After Birth**	**181 Days After Birth to the End of the Study**
Visit Window (Days)	**As Soon as Possible After Confirmed MA-RTI and Within 72 Hours**	**As Soon as Possible After Confirmed MA-RTI and Within 72 Hours**
Type of Visit	**Hospital, Home, or Clinic**	**Hospital, Home, Clinic, or Telephone**
Record concomitant medication associated with the treatment of the MA-RTI	X	X
Record adverse events, NDCMCs, and SAEs, as appropriate[g]	X	X
Obtain standard-of-care records and complete CRF[h]	X	X
Compile MA-RTI visit source documentation[i]	X	X (for *hospitalized RTIs or severe MA-LRTIs only*)

Abbreviations: CRF = case report form; ICU = intensive care unit; IV = intravenous; MA-LRTI = medically attended lower respiratory tract illness; MA-RTI = medically attended respiratory tract illness; NAAT = nucleic acid amplification technology; NDCMC = newly diagnosed chronic medical condition; RSV = respiratory syncytial virus; RTI = respiratory tract illness; RT-PCR = reverse transcription–polymerase chain reaction; SpO_2 = oxygen saturation.

a. If the infant participant is reported to be experiencing or has had an MA-RTI from birth until Visit 3, the site should arrange a study visit as soon as possible and within 72 hours. Ideally, the MA-RTI assessment visit will be conducted at the investigational study site; however, it is possible that the visit could be conducted in another healthcare setting (for example, if the infant participant is hospitalized) or the site staff may visit where the infant participant is residing.
b. If the infant participant is reported to be experiencing or has had an RTI associated with severe LRTI criteria or been hospitalized for an RTI from Visit 3 until the end of study participation, the site should arrange a visit as soon as possible and within 72 hours of site awareness. Ideally, assessment of these potential endpoint events (hospitalization due to RTI or severe MA-LRTI) will be conducted at the investigational study site; however, it is possible that the visit could be conducted in another healthcare setting (for example, if the infant participant is hospitalized) or the site staff may visit where the infant participant is residing.
Note: *For nonsevere MA-RTIs, a telephone contact with the infant participants' parent(s) or legal guardian(s) is acceptable to complete the assessment visit.*
c. Hospitalization due to an RTI and severe MA-LRTI endpoint definitions are detailed in Table 1.
d. The site staff/field worker will review and collect data related to any local NAAT testing results, if performed and available.
e. The site staff/field worker will collect nasal swabs for confirmed MA- RTIs, including confirmed cases of hospitalizations due to an RTI and severe MA-LRTIs, within 72 hours after the event is reported.
f. Background factors as detailed in Appendix 5 related to socioeconomic and health factors that may impact the incidence of RSV. This will be collected for all MA-RTI events reported.
g. The investigator and site staff/field worker will ensure the active elicitation and collection of NDCMCs and SAEs through the end-of-study visit for the infant participant. From 29 days after birth until the infant participant completes the study, NDCMCs and SAEs will be collected. 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 (eg, asthma). **Note**: *A confirmed MA-RTI will not be captured as a safety event, unless the investigator or an appropriate designee deems it to be related to the investigational product.*
h Obtain case records, including details of hospitalization, ICU, use of oxygen, IV fluids usage, etc.
i. Documents to be submitted upon request to the adjudication committee.

2. INTRODUCTION

Prevention of RSV disease in young infants is a significant unmet medical need globally. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in those with risk factors including premature infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems.[1] However, most cases of RSV disease occur in healthy, full-term infants without risk factors.[2] Worldwide, RSV kills approximately 118,200 children annually, with about half of those deaths occurring in infants under 6 months of age, and the majority of those occurring in resource-limited countries.[3,4] In the United States, RSV is the leading cause of infant hospitalization, with more than 60,000 hospitalizations of children 12 months of age and younger annually.[5,6] There is increasing evidence that the link between severe RSV disease in infancy and wheezing later in childhood may be causal.[7,8] Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall.[9] Infection is essentially universal by the time children reach 2 years of age.[10]

Currently, there is neither specific treatment for RSV infection nor a vaccine to protect against RSV disease. Treatment consists primarily of supportive care. A prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), targeting the RSV F glycoprotein is available for prevention of severe RSV disease in young infants at increased risk.[11] Limitations of its use include its high cost[12] and requirement of multiple monthly injections,[13] and so it remains recommended for use only in very premature infants and others at increased risk of severe illness.[6,14]

Nevertheless, the protective effect of Synagis provides definitive proof of principle that serum neutralizing antibody directed against the F protein can provide clinically meaningful protection against RSV lower respiratory tract disease in young infants.[15] Furthermore, it is well known that in other disease settings, antibodies transferred from mothers to their fetuses across the placenta can reduce infant disease early in life,[16,17,18,19,20,21] suggesting that maternal immunization is a reasonable approach to RSV disease prevention among young infants.

There are 2 antigenic variants of RSV, namely, RSV subgroup A (RSV A) and RSV subgroup B (RSV B). The RSV vaccine being investigated in this study is a bivalent vaccine composed of stable RSV prefusion F antigens representing the 2 subgroups to help ensure the broadest coverage against RSV illness.

RSVpreF is a prophylactic vaccine being developed to prevent medically attended RSV-associated LRTI in infants by active immunization of pregnant women.

2.1. Study Rationale

There is a large unmet medical need that could be addressed by an effective RSV prophylaxis in infancy. Given a global burden of disease in the millions of cases each year, maternal immunization offers an attractive strategy for infant disease prevention. Both preclinical studies in animals and interim data from a Phase 1/2 study in healthy nonpregnant adults

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have demonstrated acceptable tolerability and safety of RSVpreF. A robust immune response has also been observed in the population of the aforementioned trial, at 1 month after vaccination. The combined RSV A and B serum neutralization geometric mean titers (GMTs) have been shown to be 12 to 20 times higher than those with 100 µg/mL of palivizumab, the concentration of the monoclonal antibody that is known to provide near to complete protection of high-risk infants from severe RSV disease.[22,23] RSVpreF is currently under assessment in healthy pregnant women 18 through 49 years of age (Study C3671003, *A Phase 2b, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of an RSV Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants; ClinicalTrials.gov identifier: NCT 04032093)*.

This randomized, double- or observer-blinded, placebo-controlled Phase 3 study is designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended RSV-associated LRTI in infants.

2.2. Background

RSV is an important cause of morbidity and mortality worldwide, with a substantial burden of disease borne by young infants. Rates of severe RSV illness are highest in infants <6 months of age, with a peak in hospitalization between 1 and 2 months of life, though the highest case-fatality rates are observed in the neonatal period (<1 month).[2] Infants born prematurely and those with underlying cardiac or pulmonary disease are at further increased risk of severe clinical disease due to RSV. A 2017 retrospective case analysis that examined RSV mortality data from 23 countries demonstrates the global nature of the seriousness of RSV disease, with significant morbidity and mortality occurring in both lower- and middle-income countries (LMICs) and high-income countries.[3,4]

No specific treatments for RSV exist, and available prophylactic measures (ie, RSV monoclonal antibody) are limited to use in only those infants at highest risk; additionally, in LMICs, use of available RSV prophylaxis is cost-prohibitive. While active immunization against RSV in infants might be an option, multiple efforts, extending over half a century, to develop a safe and effective RSV vaccine to protect infants from disease have yielded little success. The early peak of disease presents a further obstacle to an active vaccination strategy for infants. Given these challenges, maternal immunization to protect infants early in life offers an attractive strategy for infant disease prevention.

The present RSV vaccine efforts were initiated in early 2014 based on a new scientific discovery (determination of the RSV prefusion F crystal structure)[24] and a changing regulatory and policy environment that today supports the development of vaccines for maternal immunization to protect very young infants. The trimeric RSV F surface glycoprotein in a prefusion conformation is now known to be the primary target of neutralizing antibodies and is the basis for the engineered antigens in Pfizer's vaccine candidate. Applying structure-guided vaccine design, Pfizer has developed a stabilized RSV prefusion F vaccine candidate. The core hypothesis underlying Pfizer's RSV vaccine development effort for prevention of infant disease is that vaccine antigens based on RSV prefusion F, when administered to pregnant women in the second or third trimester of pregnancy, will elicit sufficiently high neutralizing antibody titers that, when the antigens are

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actively transferred transplacentally to the fetus, will protect infants against RSV disease. The aim is for neutralizing antibody levels to be at sufficient levels such that infants will be protected from birth and possibly through their first RSV season.

2.3. Benefit/Risk Assessment

RSVpreF is being evaluated in ongoing clinical studies. Pfizer's maternal immunization approach circumvents the risk of vaccine-mediated disease enhancement that was observed in the 1960s following direct immunization of RSV-naive infants with a formalin-inactivated RSV vaccine (FI-RSV).[25] FI-RSV elicited a predominantly nonneutralizing antibody response and a Th2-biased cell-mediated response, both of which are considered potential contributing factors to disease enhancement.[26] During preclinical studies, in a standard cotton rat infectious RSV challenge model, FI-RSV showed pathological signs of causing disease enhancement, and the current Pfizer vaccine candidate, RSVpreF, did not. Most important, RSV vaccine–mediated disease enhancement has not been reported to occur in RSV-experienced individuals after immunization with any RSV vaccine candidate. Because pregnant women are universally RSV-experienced, they are not at risk for a disease-enhancing immune response to the vaccine that could exacerbate infection in themselves or their infants. A previous study of maternal immunization with a Wyeth (later merged with Pfizer) investigational RSV vaccine (PFP-2) showed an acceptable safety profile, even though this candidate contained a postfusion RSV F antigen that elicited a relatively weak RSV-neutralizing antibody response and a higher nonneutralizing RSV-binding antibody response in pregnant women.[27] A recently completed Phase 3 maternal RSV trial (Novavax) with an RSV vaccine containing F not stabilized in the prefusion form, given to over 4600 healthy pregnant volunteers, showed a similar safety profile in the RSV vaccine and placebo groups.[28]

Vaccination with the RSV prefusion F antigens elicits a higher ratio of neutralizing to nonneutralizing antibodies, more closely matching the profile in naturally exposed individuals. The safety profile of RSVpreF observed to date is similar to that of prior RSV F subunit vaccines tested in RSV-experienced adults.

There are limited data on the global burden of maternal RSV infection, likely in part because of infrequent diagnostic testing. However, in one multisite study, RSV-associated disease in pregnancy was shown to result in prolonged hospitalization and an increased likelihood of preterm birth in women who tested RSV-positive.[29] It is possible that vaccination may benefit the pregnant women who receive it. RTI in mothers who receive RSVpreF will be explored in this study. The benefit of maternal vaccination is accrued to the infant by means of transplacental antibody transfer.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of RSVpreF may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

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3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. Infant Participants

The study objectives and endpoints for infant participants employ the event definitions in Table 1.

Table 1. Endpoint Events and Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
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 laboratory with NAAT for RSV
MA-RTI due to RSV[b]	• An MA-RTI visit **AND** • RSV-positive test result as described in Section 8.1.1.1.
MA-LRTI due to any cause	• Infant with an MA-RTI visit **AND** • Fast breathing (RR ≥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
MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 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.
Hospitalized RTI due to RSV[b]	An RTI due to RSV that results in hospitalization

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Table 1. Endpoint Events and Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
Severe MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥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 (ie, 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
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by an EAC

Abbreviations: bpm = breaths per minute; 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 technology; RR = respiratory rate; RSV = respiratory syncytial virus; RTI = respiratory tract illness; SpO_2 = oxygen saturation.

a. RSV-positive testing is defined as a positive RSV test (see Section 8.1.1.1) conducted on a sample obtained during the medically attended visit or within 10 days (where Day 1 is the day after the MA-RTI visit) as detailed in Section 8.11.7.

b. The EAC will determine if the endpoint criteria have been met upon review of the site source from the MA-RTI visit data collected at the study assessment visit, including RSV testing.

Study Objectives – Infant Participants

Primary Efficacy Objectives – Infant Participants	Estimands	Primary Efficacy Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

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To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
Primary Safety Objective – Infant Participants	**Estimand**	**Primary Safety Endpoints – Infant Participants**
To describe the safety of RSVpreF.	• In infant participants born to maternal participants receiving 1 dose of investigational product, the percentage of participants with each safety endpoint in each vaccine group.	• Specific birth outcomes. • AEs from birth to 1 month of age. • SAEs and NDCMCs: o from birth through 6 months of age *(first RSV season for all infant participants).* o from birth through 12 months of age *(for all infant participants).* o from birth through 24 months of age *(for infant participants born to maternal participants enrolled during the first year of the study).*
Secondary Efficacy Objectives – Infant Participants	**Estimands**	**Secondary Efficacy Endpoints – Infant Participants**
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Hospitalization due to RSV: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

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To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	MA-LRTI due to any cause with protocol-defined criteria: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
Exploratory Objectives – Infant Participants	**Estimands**	**Exploratory Endpoints – Infant Participants**
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI due to RSV.		RSV-positive MA-RTI as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth. • occurring within 150 days after birth. • occurring within 180 days after birth. • occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.		Hospitalization due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV in infants after 6 months of age.		Severe MA-LRTIs due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.		MA-LRTIs due to any cause occurring 181 to 730 days after birth.
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.		RSV subgroup A– and subgroup B–specific MA-LRTI as confirmed by the EAC occurring within 181 days after birth.
To describe the non-RSV infectious etiology of MA-RTI in the study population.		Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits occurring within 181 days after birth.

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To evaluate RSV-neutralizing antibody titers elicited by RSVpreF and transferred transplacentally.		RSV A– and RSV B–neutralizing antibody titers measured at birth.
To assess the impact of RSVpreF on RSV illness based on socioeconomic factors.		Primary and secondary efficacy by select demographic risk factors (eg, breastfeeding, maternal smoking, number of household members).
To assess the effect of RSVpreF on healthcare utilization.		Mean/median composite score summarizing healthcare utilization, 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.

3.2. Maternal Participants

The study objectives and endpoints for maternal participants employ the event definitions in Table 2.

Table 2. Endpoint Events and Definitions in Maternal Participants

Study Endpoints/Assessments	Study Definitions
Maternal medically attended visit	The maternal participant reports a visit with a healthcare provider (outpatient or inpatient visit, emergency room, urgent care, or home visit)
MA-RTI visit 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.

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Study Objectives – Maternal Participants

Primary Safety Objective – Maternal Participants	Estimands	Primary Safety Endpoints – Maternal Participants
To describe the safety and tolerability of RSVpreF.	In maternal participants receiving 1 dose of investigational product, the percentage of maternal participants with each safety endpoint in each vaccine group.	The incidence of: • 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 (*Visit 1 through the 6-month-postdelivery study visit*).
Exploratory Objectives – Maternal Participants	**Estimands**	**Exploratory Endpoints – Maternal Participants**
To describe MA-RTI in this study population.		The incidence of all-cause MA-RTIs from vaccination up to 180 days after delivery.
To evaluate the immune responses elicited by RSVpreF.		• RSV A– and RSV B–neutralizing antibody titers and preF IgG titers measured: • before vaccination. • at delivery.

3.3. Protocol-Defined Efficacy Endpoints

All infant participants experiencing an MA-RTI will have an RTI assessment visit as detailed in Section 8.1. This protocol will use an independent EAC to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria as summarized in Table 1. Members of this EAC will be blinded to the vaccine assignment to allow for unbiased assessments.

Recognizing that RSV disease is a dynamic illness, sites will be instructed to submit all available source documentation for adjudication from the MA-RTI visit and to record data from the worst day of illness in the electronic case report form (eCRF). The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTI visit, including data collected at the study visit, and all available RSV testing. Further information about the EAC will be detailed in the adjudication charter, including specific descriptions of the scope of its responsibilities and the process and definitions to review and assess study endpoints.

MA-RTI events that are consistent with the clinical and RSV testing endpoint definition and constitute a study endpoint will not be recorded as AEs. For those SAEs that are handled as disease-related efficacy endpoints (which may include death), a data monitoring committee (DMC) will conduct unblinded reviews on a regular basis throughout the trial (see the Data Monitoring Committee section).

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Nonendpoint events (eg, an event that is determined not to be an MA-RTI) must be evaluated for safety reporting as per the protocol requirements. Any SAE that is adjudicated by the EAC **not** to meet endpoint criteria is reported back to the investigator site of incidence; the investigator at the site must evaluate and report that SAE to Pfizer Safety, in accordance with the time frames described in Appendix 2 of this protocol. The investigator's SAE awareness date in this instance is identified as the date on which the investigator site of incidence receives the nonendpoint SAE back from the EAC. Handling these SAEs in this manner will allow Pfizer to meet its sponsor reporting obligations to regulatory authorities upon receipt of such SAEs.

However, when the investigator has judged the SAE to have a causal relationship with the investigational product, the investigator must additionally report the event to Pfizer Safety as described in Appendix 2, even if that event is a component of the endpoint.

Any events that remain unadjudicated at the annual safety report cutoff date will not be included in the safety tables of the report.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, double- or observer-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, as well as 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 the statistical analysis (Section 9.2). There is no specific case target for the additional primary endpoint of severe MA-LRTI. The total enrollment number of maternal participants may vary depending on the incidence rate of the primary endpoint in the infant participants, true underlying VE, and a potential early stop for efficacy or futility. In the event that efficacy in the infant population is demonstrated at the interim analysis, enrollment of maternal participants may continue in order to obtain safety evaluations in an adequate number of maternal and infant participants to support vaccine registration with national health authorities.

Based on these considerations, and in order to accumulate endpoint cases, 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 is anticipated that approximately 6900 mother-infant pairs may be needed to accumulate 124 per-protocol cases.

Study-eligible pregnant women will be randomized in a 1:1 ratio to receive RSVpreF or placebo. For the RSV vaccine group, a single dose and formulation of RSVpreF will be selected based on data from the maternal C3671003 study *(A Phase 2b, Randomized, Placebo-Controlled, Observer-Blind Trial to Evaluate the Safety, Tolerability, and*

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Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants. ClinicalTrials.gov identifier: NCT 04032093). The selected dose of RSV prefusion F antigen in RSVpreF will be 120 µg (60 µg A and 60 µg B) or 240 µg (120 µg A and 120 µg B). The selected formulation will be with or without $Al(OH)_3$.

Once they have provided informed consent, the women will be referred to as "maternal participants" and will be followed from vaccination during pregnancy until 6 months after delivery. Assessments will include parameters to allow descriptions of safety, tolerability, and immunogenicity of the vaccine in maternal participants.

Infants born to women who receive RSVpreF or placebo in their second or third trimester will be referred to as "infant participants". Infant participants born to women enrolled during the first year of the study will have 6 scheduled study visits during their 24 months of participation, whereas all other infant participants will have up to 4 scheduled study visits during their potential 12 months of participation. 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. For infant participants enrolled during the first year of the study, the extended 12-month study duration will involve 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 MA-RTIs meeting the protocol definition for a potential study endpoint will be adjudicated by an independent adjudication committee. In addition, this study will use an E-DMC to monitor vaccine safety and efficacy and study futility.

4.1.1. Approximate Duration of Participation for Each Participant

Pregnant women will participate in the study from enrollment during their pregnancy, and for approximately 6 months after delivery of their infants. The total duration will be up to approximately 10 months, depending on GA at the time of vaccination and when the infant is actually born.

All eligible infant participants born to enrolled maternal participants during the first year of the study will participate in the study from the time of birth and will be followed for up to 24 months for RSV surveillance and safety for the secondary and exploratory endpoints of the study. All other infants will participate from the time of birth and for at least 12 months after birth.

4.1.2. Approximate Number of Participants

Healthy pregnant women will be randomly assigned to a study intervention. It is anticipated that approximately 6900 mother-infant pairs may be needed to accumulate 124 per-protocol cases as defined in Section 9.2 of the protocol. Enrollment will be monitored to ensure that participants will be recruited from both the northern and southern hemispheres. Enrollment may vary depending on the incidence in the placebo group, the true underlying VE, the dropout rate, and a potential early stop for VE or futility.

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4.2. Scientific Rationale for Study Design

Refer to Section 2.1.

4.3. Justification for Dose

The final dose and formulation of RSVpreF that will be selected for use in this study will be based on the safety and immunogenicity data from the ongoing C3671003 maternal immunization study and the first-in-human (FIH) study C3671001.

The FIH study was designed to describe the safety, tolerability, and immunogenicity of 6 RSVpreF candidates with bivalent formulations (RSV A and B) at 3 escalating dose levels of 60 µg (30 µg A and 30 µg B), 120 µg (60 µg A and 60 µg B), and 240 µg (120 µg A and 120 µg B) of the RSV prefusion F antigen, with or without $Al(OH)_3$, when administered alone or concomitantly with seasonal inactivated influenza vaccine. The study utilizes a sentinel cohort (N=168; Phase 1) and an expanded cohort (N=1014; Phase 2). Nonpregnant female and male study participants of 2 age groups, 18 through 49 years of age and 50 through 85 years of age, were enrolled into both cohorts. The age groups are being run in parallel.

A recent interim analysis of participants 18 through 49 years of age, including safety and tolerability (n=533) and immunogenicity (n=513) data up to 1 month after vaccination in the expanded cohort and additional immunogenicity data up to 3 months after vaccination in the sentinel cohort, has shown the RSVpreF candidate to be immunogenic and well tolerated.

Local reactions and systemic events were noted to be predominantly mild or moderate across all doses and formulations, which is consistent with the current safety profile. The safety results from this planned interim analysis of healthy male and nonpregnant female participants 18 through 49 years of age are consistent with those from the sentinel-cohort analysis and indicate that RSVpreF has an acceptable safety profile and is well tolerated.

The immunogenicity results showed that RSVpreF elicited neutralizing titer geometric mean fold rises (GMFRs) of 10 to 20, 1 month after vaccination, depending on the formulation. Similarly, across all dose levels, with and without $Al(OH)_3$, RSVpreF elicited high 1-month-postvaccination RSV A and RSV B neutralizing GMTs. Overall, RSVpreF elicited anti–prefusion F immunoglobulin G1 (IgG1) responses that paralleled the elicited RSV-neutralizing responses. The ratio of RSV 50% neutralizing antibody titer GMFRs to prefusion RSV F binding IgG1 titer GMFRs (calculated with combined data for subgroups A and B) for the sentinel and expanded 18 through 49 years of age cohorts combined ranged from 0.62 to 0.76. The IgG1 and neutralization responses were similar in antigen-level dose response, in equivalence of RSV A titer GMFRs to RSV B titer GMFRs, and in a lack of effect of $Al(OH)_3$.

The high ratio of RSV-neutralizing antibody titer GMFRs to prefusion F–binding titer GMFRs elicited by Pfizer's RSVpreF candidate indicates that most of the elicited antibody can neutralize the virus. It is assumed that this reflects the ability of the antibodies to prevent RSV disease in immunized participants and, in the case of maternal immunization, prevent disease in their infants.

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The primary mechanism for protection of infants by the RSV maternal vaccine is neutralization of the virus by transplacentally transferred antibody, which is increased by immunization. Maternal antibody decays exponentially in infants. Therefore, it is anticipated that higher titers of transferred neutralizing antibodies will provide greater levels and durations of infant protection. Results from the C3671001 FIH trial were used to determine the doses and formulations that are currently under investigation in the Phase 2b maternal immunization study: 120 µg or 240 µg of RSVpreF with or without $Al(OH)_3$. These doses are expected to provide the greatest potential level of transplacental antibody transfer to infants and, therefore, the greatest potential benefit. One-month safety, tolerability, and immunogenicity results from the C3671003 maternal Phase 2b trial will be used to select a single dose and formulation for the Phase 3 study. Availability of these data is expected in 2020.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last infant participant in the study. The study may also be terminated earlier for efficacy or futility as described in Section 9.5.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria – Maternal Participants

Participants are eligible to be included in the study only if all of the following criteria apply (refer to the investigator site file [ISF] for further eligibility details):

Note: In countries/locales where study procedures used to determine eligibility criteria (eg, ultrasound examination, human immunodeficiency virus [HIV] testing, syphilis testing) are not performed as part of routine prenatal care, they must be performed as part of this clinical trial and reviewed by the investigator or qualified designee within 28 days prior to randomization. **Maternal participants must provide informed consent prior to performing any procedures, including those that are being done exclusively to meet study eligibility criteria.**

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Age and Sex:

1. Healthy women ≥18 and ≤49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications.

   Note: GA must be based upon 1 of the following composite criteria based on timing and availability of data on the last menstrual period (LMP) and an ultrasound examination performed in the first or second trimester.[30] The earliest ultrasound data available during the current pregnancy should be used to establish GA:

   a. **First-trimester data available** (data obtained at ≤13 6/7 weeks):

      - The date of the first day of the reported LMP may be used to establish the GA if corroborated by a first-trimester ultrasound examination.
      - If there is a discrepancy of >5 days between the LMP-determined GA and an ultrasound result at ≤8 6/7 weeks OR the LMP is uncertain/unknown, then the GA should be determined using the first-trimester ultrasound result.
      - If there is a discrepancy of >7 days between the LMP-determined GA and an ultrasound result at 9 0/7 to 13 6/7 weeks OR the LMP is uncertain/unknown, then the GA should be determined using the first-trimester ultrasound result.

   b. **Second-trimester data available** (data obtained at 14 0/7 to 27 6/7 weeks):

      - The date of the first day of the reported LMP may be used to establish the GA if corroborated by a second-trimester ultrasound result.
      - If there is a discrepancy of >7 days between the LMP-determined GA and the ultrasound result at 14 0/7 to 15 6/7 weeks OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound result.
      - If there is a discrepancy of >10 days between the LMP-determined GA and the ultrasound result at 16 0/7 to 21 6/7 weeks OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound result.
      - If there is a discrepancy of >14 days between the LMP-determined GA and the ultrasound result at 22 0/7 to 27 6/7 weeks OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound result.

Type of Participant and Disease Characteristics:

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

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

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

5. Determined by medical history, physical examination, and clinical judgment to be appropriate for inclusion in the study.

6. Documented negative HIV antibody test, syphilis test, and hepatitis B virus (HBV) surface antigen test during this pregnancy and prior to randomization (Visit 1).

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

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

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

Informed Consent:

10. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol **OR**

11. If the maternal participant is illiterate, a thumbprinted informed consent must be obtained, which must be signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant has been informed of all pertinent aspects of the study.

5.1.2. Inclusion Criteria – Infant Participants

1. Evidence of a signed and dated ICD signed by the parent(s)/legal guardian(s) **OR**

   If the infant participant's maternal participant/parent(s)/legal guardian(s) is illiterate, a thumbprinted informed consent must have been obtained, which must have been signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant/parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study for herself (maternal participant) and her fetus/infant prior to taking part in the study.

   Note: Informed consent will be obtained from the father of the fetus/infant if mandated by local requirements.

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

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5.2. Exclusion Criteria

5.2.1. Exclusion Criteria – Maternal Participants

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

Weight:

1. Body mass index (BMI) of >40 kg/m^2 at the time of the first obstetric visit during the current pregnancy.

Medical Conditions:

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

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

4. Current pregnancy resulting from in vitro fertilization. *Participants known to have used clomiphene citrate and/or letrozole with or without IUI are permitted.*

5. Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following (refer to the ISF for further details):

    - Preeclampsia, eclampsia, or uncontrolled gestational hypertension.
    - Placental abnormality.
    - Polyhydramnios or oligohydramnios.
    - Significant bleeding or blood clotting disorder.
    - Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism. This also includes disorders of glucose intolerance (eg, diabetes mellitus type 1 or 2) antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent.
    - Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth.

6. Prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:

    - Prior preterm delivery ≤34 weeks' gestation.

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- Prior stillbirth or neonatal death.
- Previous infant with a known genetic disorder or major congenital anomaly.

7. Major illness of the maternal participant or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the maternal participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response.

8. Congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrollment.

9. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

10. Participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation.

11. Receipt of monoclonal antibodies within the year prior to enrollment or the use of systemic corticosteroids for >14 days within 28 days prior to study enrollment. *Prednisone use of <20 mg/day for ≤14 days is permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.*

12. Current alcohol abuse or illicit drug use.

13. Receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (eg, RhoGAM), which can be given at any time.

Prior/Concurrent Clinical Study Experience:

14. Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation.

Diagnostic Assessments:

Not applicable.

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Other Exclusions:

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

16. Participants who are breastfeeding at the time of enrollment.

5.2.2. Exclusion Criteria – Infant Participants

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

2. Receipt of investigational or approved monoclonal antibodies against RSV.

5.2.3. Temporary Vaccination Delay Criteria – Maternal Participants

The following conditions are temporary or self-limiting and a maternal participant may be vaccinated once the condition(s) has/have resolved and if no other exclusion criteria are met. The prevaccination blood draw and vaccination should take place on the same day.

- Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before investigational product administration.

- Diagnosed malaria within the last 7 days prior to investigational product administration.

- Receipt of any inactivated vaccine within 14 days or any live vaccine within 28 days before investigational product administration.

- If systemic corticosteroids (equivalent of ≥20 mg/day of prednisone) have been administered short term (≤14 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

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

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6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational product(s) are RSVpreF and placebo (lyophile match).

6.1.1. Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. There are 2 presentations of RSV drug product representing 2 dose levels of RSV antigen (120 µg and 240 µg). The drug product is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The drug product is reconstituted by diluent consisting of either sterile water as diluent prefilled syringe (PFS) or $Al(OH)_3$ 0.4-mg/mL suspension for injection PFS. The lyophilized drug product contains excipients that, after reconstitution, will yield a solution as detailed in Table 3.

Note: Only 1 dose and formulation of RSVpreF will be selected for use in this study.

The fill volume of the drug product vial and diluent PFS are designed such that the intended vaccine dose is delivered in a 0.5-mL injection volume.

Table 3. Composition of the RSV Vaccine Intended for Clinical Evaluation After Reconstitution With Diluent

Formulation	120-µg Antigen Dose		240-µg Antigen Dose	
	Without $Al(OH)_3$ (mg/mL)	With $Al(OH)_3$ (mg/mL)	Without $Al(OH)_3$ (mg/mL)	With $Al(OH)_3$ (mg/mL)
847 A DS	0.12	0.12	0.24	0.24
847 B DS	0.12	0.12	0.24	0.24
Tromethamine base	0.23	0.23	0.23	0.23
Tris-hydrochloride	2.07	2.07	2.07	2.07
Sucrose	22.5	22.5	22.5	22.5
Mannitol	45.0	45.0	45.0	45.0
NaCl	2.19	5.55	2.19	5.55
Polysorbate 80	0.15	0.15	0.15	0.15
$Al(OH)_3$	N/A	0.4	N/A	0.4

Abbreviations: $Al(OH)_3$ = aluminum hydroxide; DS = drug substance; N/A = not applicable; NaCl = sodium chloride.
Note: A single dose and formulation of RSVpreF will be selected based on data from the maternal C3671003 study (NCT: 04032093).

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6.1.2. Placebo

Placebo will be a lyophile match to the vaccine, which will consist of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients.

If the final RSVpreF formulation without $Al(OH)_3$ is selected, the physical appearance of the reconstituted RSVpreF and placebo will be matched and the study will be conducted in a double-blinded manner.

In the event that the RSVpreF formulation with $Al(OH)_3$ is selected, the reconstituted placebo will not contain $Al(OH)_3$. The physical appearance of the reconstituted RSVpreF and the placebo will differ, and the study will be conducted in an observer-blinded manner.

The fill volume of the placebo vial and diluent PFS is designed such that the intended placebo dose is delivered in a 0.5-mL injection volume.

Placebo will be provided by the sponsor to each study site. The placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

6.1.3. Administration

Maternal participants will receive 1 dose of investigational product at the vaccination visit (Day 1) in accordance with the study's SoA. The investigational product will be administered intramuscularly by injecting the entire contents of the syringe (0.5 mL) into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Investigational product administration will be performed by appropriately designated study staff at the investigator site.

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

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

Investigational product administration details will be recorded on the case report form (CRF).

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6.1.4. Medical Devices

In this study, medical devices being deployed are for the reconstitution diluents for the RSV vaccine or placebo, consisting of either sterile water PFS or $Al(OH)_3$ 0.4-mg/mL suspension for injection PFS.

Instructions for medical device use are provided in the IP manual.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the unblinded study personnel throughout the study.

Please refer to Section 8.3.6 for details.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

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

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product manual (IP manual).

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. See the IP manual for storage conditions of the study intervention once reconstituted.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue

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options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

   Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

Refer to the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Investigational product and placebo will be prepared by qualified site personnel according to the IP manual. The investigational product will be administered only to maternal participants who are blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Blinding of Study Site Personnel

This study is a double- or observer-blinded study, as the physical appearance of RSVpreF and placebo may differ.

Double-Blinded Study Personnel
If this is a double-blinded study, the physical appearance of RSVpreF and placebo will be matched. The maternal participant, investigator, study coordinator, and all site staff will be blinded.

Observer-Blinded Study Personnel
If this is an observer-blinded study, the physical appearance of RSVpreF and placebo will not be matched. At the study site, only the dispenser(s)/administrator(s) will be unblinded, but all other study personnel, including the investigator and study coordinator, and the maternal participant will be blinded.

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Contact between the unblinded dispenser(s)/administrator(s) and maternal participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispenser(s)/administrator(s) must not be allowed to know the investigational product assigned to any maternal participant and must not be allowed to see the investigational product.

Please refer to the IP manual for further details.

6.3.2. Blinding of the Sponsor

The sponsor study team members will be blinded throughout the study to the vaccine assignments of all participants enrolled in the study.

Laboratory personnel performing the serology and virology assays will remain blinded to vaccine assigned/received throughout the study.

6.3.3. Allocation to Investigational Product

Allocation of maternal participants to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the maternal participant number. The site personnel will then be provided with a vaccine assignment, randomization number, and dispensable unit (DU) or container number as investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the maternal participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Note: Maternal participants will be randomized to a vaccine group as described above. The infants of the maternal participants will be assigned an infant participant number at birth.

Investigational product will be dispensed and administered at study Visit 1 summarized in the SoA.

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

Maternal participants will be assigned to receive investigational product according to the randomization scheme. Investigators will remain blinded to the investigational product assigned to each maternal participant throughout the course of the study. Based on observer-blinded considerations for this study, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all investigational product and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation of the investigational products following randomization.

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In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded investigational product records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.4. Breaking the Blind

The study will be maternal participant and investigator blinded.

At the initiation of the study, the investigator will be instructed on the method for breaking the blind for an individual participant. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. The investigators should make every attempt to contact a member of the sponsor's study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

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

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

6.5.1. Prohibited Concomitant Vaccinations and Treatments – Maternal Participants

- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.
- Receipt of blood/plasma products or Ig, from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (eg, RhoGAM), which can be given at any time.
- Immunosuppressive therapy is prohibited during the course of the study.
- Nonstudy vaccines may not be given concomitantly with the investigational product or within 7 days after investigational product administration (Day 1 to Day 7), except if medically necessary (eg, during an outbreak or pandemic situation).

6.5.2. Permitted Concomitant Vaccinations and Treatments – Maternal Participants

- Licensed vaccines (including influenza vaccine and tetanus, diphtheria, and acellular pertussis vaccine [Tdap]) may be given during the study starting 7 days after investigational product administration (Day 8) as per local recommendation for immunization in pregnant women. If medically necessary (eg, during an outbreak or pandemic situation), influenza vaccine, Tdap, or other vaccines may be given at any time.

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Note: The restricted timelines around the use of Tdap may be dropped based on data from the C3671004 study (*A Phase 2b, Placebo-Controlled, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine When Administered Concomitantly With Tetanus, Diphtheria, and Acellular Pertussis Vaccine (Tdap) in Healthy Nonpregnant Women 18 Through 49 Years of Age*).

- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. Prednisone use of <20 mg/day for ≤14 days prior to the administration of investigational product is permitted.

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during participant participation in the study.

6.5.3. Recording Nonstudy Vaccinations and Concomitant Medications – Maternal Participants

The following vaccinations and treatments for maternal participants would require reporting in the CRF during the study:

- Details of any vaccinations given at any time during the pregnancy through the final study visit will be collected and recorded in the CRF.

- Details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given to the maternal participant at any time during the pregnancy or during the study will be collected and recorded in the CRF.

    - Details of any **intrapartum antibiotic prophylaxis (IAP) for maternal group B streptococcal (GBS) colonization** given to the maternal participant at delivery will be collected and recorded in the CRF.

- Any **prescribed** medications taken to treat medically attended respiratory illnesses from enrollment until the final study visit will be recorded in the CRF.

Concomitant medications not meeting the criteria above will be assessed but not documented on the CRF.

6.5.4. Permitted Concomitant Vaccinations and Treatments – Infant Participants

- Routine treatments, routine vaccinations, and routine procedures (eg, circumcision) are permitted at any time according to national recommendations or medical standard of care or accepted practice.

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

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

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6.5.5. Recording Nonstudy Vaccinations and Concomitant Medications – Infant Participants

The following CRF reporting guidelines are applicable to treatments given to infant participants during the study:

- Details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, hepatitis B immune globulin (HBIG)]) or blood products (eg, whole blood, packed cells) given to the infant participant will be collected from the time of birth until the final study visit and recorded in the CRF.

- Any **prescribed** medication taken to treat medically attended respiratory illnesses from the time of birth until the final visit.

- Details of IV fluids given during an MA-RTI will be collected and recorded in the CRF.

6.6. Dose Modification

Dose modification is not applicable in this study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Discontinuation of study intervention is not applicable in this study.

7.2. Participant Discontinuation/Withdrawal From the Study

A maternal participant may withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. An infant participant may withdraw from the study at any time at the request of his or her parent(s) and/or legal guardian(s) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The participants, or, if appropriate, their parent(s) and/or legal guardian(s), should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a maternal participant withdraws from the study, she may request destruction of any remaining samples, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses. If an infant participant is withdrawn from the study, his or her parent(s) and/or legal guardian(s) may request destruction of any remaining samples, but data already generated from the samples will

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continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

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

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

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

Participants who withdraw after randomization will not be replaced.

7.3. Withdrawal of Consent

Maternal participants and parent(s)/legal guardian(s) of infant participants born to maternal participants who request to withdraw consent from any further study contact or with persons previously authorized by the participant to provide this information should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from study procedures and/or postvaccination study follow-up. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

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

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- Should the participant or parent(s) and/or legal guardian(s) continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

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8.1. Efficacy Assessments

8.1.1. Efficacy Assessments – Infant Participants

MA-RTIs in the infant participant will be identified from birth until the end of the infant's participation in the study. If the infant participant meets any RTI criteria listed below that require a visit by or a visit to a healthcare provider (outpatient or inpatient visit, emergency room, urgent care, or scheduled home visit), an RTI assessment visit by the study staff will be required (see Section 8.11.7).

The RTI criteria are if the infant experiences 1 or more of the following respiratory signs or 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 due to respiratory symptoms
- Apnea
- Any other respiratory symptom of concern

Evaluation of these MA-RTI events will be based on predefined clinical signs and symptoms and testing criteria (shown in Table 1) obtained at the medically attended visit with the healthcare provider and/or the study visit. These events will be assessed and confirmed to be contributing to the study endpoints by an independent EAC as per the protocol.

8.1.1.1. Midturbinate Nasal Swab Collection and Testing Requirements for Endpoint Confirmation – Infant Participants

Midturbinate nasal swabs will be collected for RSV analyses from infant participants at each MA-RTI study visit during the RSV surveillance period from birth until Visit 3, and for all hospitalizations due to an RTI and severe cases of MA-LRTI during the RTI surveillance period from Visit 3 until the end of the study (see Section 1.2.4.1 and Table 1). The swabs will be sent to Pfizer for centralized reverse transcription–polymerase chain reaction (RT-PCR) testing.

RSV testing performed locally as part of routine care will be considered valid when analyzed under the following conditions:

- Nucleic acid amplification technology (NAAT)-based test result positive for RSV was obtained using a Food and Drug Administration (FDA)-cleared assay.

  OR

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- NAAT-based test result positive for RSV was obtained using an assay that is not FDA cleared but was conducted in a laboratory that is currently Clinical Laboratory Improvement Amendments (CLIA) certified.

Note: Rapid antigen-based test results will not be considered for endpoint assessment.

Study samples should be collected as close to the medical visit as possible and preferably within 72 hours of the MA-RTI visit. RSV study samples will count toward the endpoint definition when collected for up to 10 days after the MA-RTI, where Day 1 is the day after the MA-RTI visit. These results will be used for MA-RTI endpoint definition and confirmation as detailed in Table 1.

8.1.1.2. Events for Adjudication and Submission Guidance – Infant Participants

To maintain scientific integrity, this protocol will use an EAC for the adjudication of all primary efficacy endpoints and death events associated with the infant participants due to any cause, as summarized below. The EAC will remain blinded to the maternal participants' vaccine assignments, and the EAC's assessment of these events will represent the final confirmed endpoint classification of the event.

The efficacy-related events for adjudication include all MA-RTI events. The study definitions for endpoint events and the MA-RTI adjudication criteria for the EAC, including roles and responsibilities, are specified in the endpoint adjudication committee charter (EACC).

The identification of an MA-RTI will be made by the investigational site and communicated to Pfizer or its designee. However, these MA-RTI events may also be identified by Pfizer or its designee during the review of clinical data listings or by site monitors during routine monitoring of the infant participants' study records. Pfizer or its designee will notify the investigational site of any events identified during this process.

The EAC is responsible for adjudicating whether MA-RTI events fulfill the protocol-defined clinical criteria as a primary endpoint, whether the event was due to RSV based on confirmatory testing, and the severity of the illness (eg, MA-RTI, MA-LRTI, or severe MA-LRTI). The EAC will adjudicate all RSV-positive MA-RTI cases through the active follow-up period including all cases occurring up to 180 days after birth. The EAC will adjudicate severe manifestations of RSV: all RSV-associated cases of hospitalization and severe MA-LRTI. All deaths will be adjudicated to determine whether they are related to RSV during the course of the study.

The Pfizer study team or designee will provide a listing of specific documents needed to support endpoint adjudication by the EAC. These documents will be detailed in the EACC and the ISF. Obtaining and submitting the documentation, including results of local testing for RSV, will be the responsibility of the investigational site. Documentation will vary based on the potential endpoint requiring adjudication and may include (but not be limited to) emergency room visit records, hospital discharge summaries, clinic and/or progress notes,

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diagnostic tests, pathology reports, autopsy reports, and death certificate information, as applicable.

Pfizer may request that additional cases of interest be reported to the committee in addition to those listed above, including cases in which RSV testing is indeterminant or otherwise unclear. Cases that are determined to be RSV positive using non–NAAT-based clinical testing can be adjudicated, explored, and summarized descriptively.

8.1.2. Exploratory Efficacy Assessments – Maternal Participants

An MA-RTI will be identified from vaccination until the end of the study and will contribute to an exploratory endpoint for maternal participants. The definition and assessment criteria as described in Section 8.10.6 include a visit by or to a healthcare provider (outpatient or inpatient visit, emergency room, urgent care, or home visit) for any symptoms in the RTI criteria as detailed in Table 2.

The maternal participant should contact the study staff immediately but no later than the next scheduled visit to report RTI signs and symptoms for which she sought medical attention. The procedures as detailed in Section 1.2.3.1 and Section 8.10.6 will be required to capture the event in the CRF.

8.1.3. Efficacy Endpoints and Safety Reporting Requirements – Maternal and Infant Participants

MA-RTI events that are consistent with the clinical and RSV testing endpoint definition for infant participants and have been adjudicated as a study endpoint (primary or secondary) by the EAC should not be recorded as AEs. These data will be captured as efficacy assessment data only, as these are expected endpoints.

For maternal participants, MA-RTI events that are consistent with the clinical and endpoint definition will be captured as detailed in Section 8.1.2 and will not be recorded as AEs.

Any SAE that the investigator has judged to have a causal relationship with the investigational product MUST be reported to Pfizer Safety as described in Appendix 2, even if that event is a component of an endpoint.

8.1.4. Immunogenicity Assessments

8.1.4.1. Total Volume of Blood Collected – Maternal Participants

The total volume of blood collected for antibody assessment over the course of the study will be approximately 30 mL (~15 mL/visit).

8.1.4.2. Total Volume of Blood Collected – Infant Participants

Blood samples will be collected according to the directive 2001/20/EC: Ethical Consideration for Clinical Trials Performed in Children.[31]

All infants will have a cord blood sample collected at birth. The cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been clamped

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and cut. Blood should be collected as soon as feasible after birth to minimize coagulation and maximize volume. **The total volume of cord blood to be collected for antibody assessment in this study will be 10 mL**.

If cord blood is unavailable, a blood sample may be collected from the infant participant up to 7 days after birth but **preferably within 24 hours after birth.** The infant's weight must be used to determine the volume of blood that can be collected (see Table 4).

A blood sample will be collected from the infant participant only if a cord sample is not obtained. In the event that a venous sample is collected, the volume of venous blood will vary depending on the infant's weight.

The maximum volume of blood collected from the infant in the absence of cord blood will be no more than 5 mL.

Table 4. Guideline for Infant Blood Draw, if Cord Blood Sample Was Not Obtained

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

8.1.4.3. RSV Vaccine Antibody Testing – Maternal and Infant Participants

Maternal sera and infant cord blood collected will be assayed for RSV A– and RSV B–neutralizing titers and anti-RSV prefusion F IgG levels. Maternal sera collected may be tested for Ig levels against nonvaccine RSV antigens to assess natural RSV exposure.

RSV A– and RSV B–neutralizing antibody titers will be determined and reported as the neutralizing titer. IgG levels will be determined against both RSV A and RSV B prefusion F antigens in a direct-binding Luminex immunoassay (dLIA) and reported as an anti–prefusion F IgG level.

Sample collection, processing, storage, and shipping information can be found in the ISF or equivalent manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

8.1.4.4. Exploratory Assays, Including Immunogenicity Assessments and Assay Development – Maternal and Infant Participants

Samples remaining after completion of the planned assays from blood draws or respiratory nasal swab specimens taken throughout the study may be used for additional vaccine and infectious disease related research. Samples may also be used for assay development, standardization, qualification, and validation. This work is critical in the development,

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qualification, and validation of serological assays and is required by regulatory authorities for their use in the licensure of a vaccine.

8.1.4.5. Respiratory Pathogens – Infant Participants

Midturbinate nasal swabs will be collected from infant participants following **any MA-RTI visit** during the RSV surveillance period from birth until Visit 3, and for **all hospitalizations due to an RTI and severe cases of MA-LRTI** during the RTI surveillance period from Visit 3 until the end of the study (see Section 1.2.4.1 and Table 1).

Samples will be analyzed for RSV A, RSV B, and other respiratory pathogens by polymerase chain reaction (PCR)-based assays at a central laboratory. Additional exploratory analyses may also be performed.

Sample collection, processing, storage, and shipping information can be found in the ISF or equivalent manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

8.1.4.6. Biological Samples – Maternal and Infant Participants

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

The maternal participant may request that her (or her infant's) samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained, and no testing of the maternal and infant participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Safety parameters will be assessed as described in the SoA and below for both maternal and infant participants.

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8.2.1. Participant Electronic Diary – Maternal Participants

All maternal participants vaccinated in the study will be observed for at least 30 minutes after investigational product administration for any acute reactions. For all maternal participants, prespecified local reactions and systemic events will be collected for 7 days after vaccination.

Maternal participants will be required to use an electronic diary (e-diary), installed on a provisioned device or as an application on a personal device, and will be asked to monitor and record local reactions, systemic events, and temperature each evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). Prior to vaccination, a baseline assessment of prespecified systemic events will be recorded in the e-diary.

The e-diary allows recording of these assessments only within a fixed time window each day, thus providing the accurate representation of the maternal participant's experience at that time.

Similarly, based on local practice in certain countries/locales, a field worker may visit maternal participants in their homes daily after vaccination to assess and record local reactions, systemic events, and temperature each day (beginning in the morning) for 6 days following vaccination (Day 2 through Day 7, where Day 1 is the day of vaccination). The field worker will be required to record these data on a provisioned device or an application on a personal device, thus providing the accurate representation of the maternal participant's experience at that time. For events persisting at Day 7 and use of antipyretic medication continuing at Day 7, the field worker will continue to visit the participant and record information until resolution.

Data on local reactions, systemic events, and temperature recorded in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be recorded by the investigator in the CRF, except the following conditions:

- If a maternal participant withdraws because of prompted events recorded in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

- The investigator or designee must obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

Investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate maternal participant compliance and as part of the ongoing safety review. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.2.1.1 and Section 8.2.1.2.

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8.2.1.1. Local Reactions – Maternal Participants

Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), the maternal participants/field worker will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary or appropriate device, in the evening or daily based on local practice.

Redness and swelling will be measured by the maternal participant/field worker 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 5. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm.

A maternal participant with severe redness, swelling, or pain at the injection site, necrosis, or exfoliative dermatitis will be prompted to contact the investigator to perform an unscheduled visit to assess the reaction or will be referred to the appropriate healthcare facility at the discretion of the field worker if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant.

Only an investigator or a qualified designee 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. If a maternal participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. A Grade 4 reaction will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.2.4).

The site staff/field worker will educate the maternal participant regarding signs and symptoms (including necrosis at the injection site or exfoliative dermatitis) that would prompt site contact.

If a local reaction persists beyond the end of the e-diary period, the maternal participant will be requested to report that information and/or any new AEs that develop to the investigator, or the field worker will continue to visit the maternal participant to assess and record the information until resolution, as per local practice. The investigator will enter this additional information in the maternal participant's source notes and CRF.

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Table 5. 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 or qualified designee is able to classify a maternal participant's local reaction as Grade 4, after clinical evaluation of the maternal participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the maternal participant. Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.4.

8.2.1.2. Systemic Events – Maternal Participants

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. Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), maternal participants will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening or, based on local practice in certain countries/locales, a field worker will visit maternal participants daily after vaccination to assess the presence of systemic events each day (beginning in the morning) for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). The field worker will record the symptoms in the e-diary daily. The symptoms will be assessed by the maternal participant according to the grading scale in Table 6. Maternal participants will also be instructed to contact site staff if they visit the emergency room or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain within 7 days after vaccination. Based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the field worker if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant. The study staff/field worker may also contact the maternal participant to obtain additional information on events entered into the e-diary.

Only an investigator or qualified designee 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. If a maternal participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected as an

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AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.2.4).

Further, if a systemic event persists beyond the end of the e-diary period, the maternal participant will be requested to report that information and/or any new AEs that develop to the investigator, or the field worker will continue to visit the maternal participant to assess and record the information until resolution, as per local practice. The investigator will enter this additional information in the maternal participant's source notes and CRF.

Table 6. 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 or qualified designee is able to classify a maternal participant's systemic event as Grade 4, after clinical evaluation of the maternal participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the maternal participant. Grade 4 systemic reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.4.

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8.2.1.3. Temperature – Maternal Participants

A digital thermometer will be given to the maternal participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) and at any time during the 7 days following vaccination that fever is suspected. Similarly, based on local practice in certain countries/locales, the field worker will visit maternal participants daily for 7 days after vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) to collect the temperature.

Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary, where possible. In certain countries/locales, if a temperature of ≥100.4°F (≥38.0°C) is recorded for a maternal participant during the collection of diary events after vaccination, the field worker will perform a rapid test for malaria as per local practice.

In the event of a fever on the last day the diary was completed, temperature will be measured daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF.

A maternal participant with a fever >102.0°F (>38.9°C) will be prompted to contact the investigator. Based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the field worker if there are any concerns, as applicable. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant. The investigator or qualified designee will assess the fever and perform an unscheduled visit as appropriate.

Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 7. Temperatures reported in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting.

Table 7. Ranges for Fever

Fever	≥38.0°C to 38.4°C	>38.4°C to 38.9°C	>38.9°C to 40.0°C	>40.0°C

8.2.2. Clinical Safety Laboratory Assessments – Maternal and Infant Participants

There are no protocol-required laboratory assessments.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the maternal participant/parent(s)/legal guardian(s).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue

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and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or caused the participant to discontinue from the study (see Section 7).

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

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

Maternal Participants

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each maternal participant including her fetus begins from the time the maternal participant provides informed consent, which is obtained before participation in the study (ie, before undergoing any study-related procedure and/or receiving 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 safety events as detailed below:

- The active collection period for nonserious AEs begins once informed consent has been provided and continues 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 AEs/SAEs 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.

Infant Participants

For the infant participant, the time period for actively eliciting and collecting safety events is detailed below:

- The active collection period for 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.

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  - Details of any MA-RTI will not be collected as AEs/SAEs from informed consent 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.** See Section 8.1 for the reporting procedures for efficacy-related endpoints. Note: Details of the MA-RTI visit should be recorded in the eCRF.

- 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.

For maternal participants, and parent(s)/legal guardian(s) of infant participants born to maternal participants, who withdraw from the study and withdraw consent for the collection of future information, the active collection period ends when consent is withdrawn.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form and the Exposure During Pregnancy Supplemental Form if applicable.

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

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

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

The same is applied for those SAEs after the active collection period has ended, should they occur to the fetus. In addition, infant deaths that occur after 12 months of age should be reported as SAEs when the investigator believes the death has at least a reasonable possibility of being related to investigational product.

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

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8.3.1.2. Recording Nonserious AEs and SAEs in the CRF

All AEs/SAEs occurring in a participant during the active collection period are recorded in the CRF.

The investigator obtains general information on the pregnancy and its outcome for all study participants. The investigator will follow the pregnancy until completion (or until pregnancy termination). In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4).

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

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

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8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

Potential efficacy endpoints on this study as defined in Section 8.1 will be excluded from the standard SAE reporting process unless deemed possibly related to investigational product.

8.3.5. Additional Exposure Scenarios That May Result From the Exposure to the Investigational Product

8.3.5.1. Exposure During Breastfeeding

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

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure-during-breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.2. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the investigational product, which may or may not lead to the occurrence of an AE.

In addition, the scenarios below describe environmental exposures that could lead to an exposure during pregnancy (EDP):

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- A female becomes or is found to be pregnant, having been exposed (eg, because of environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after being exposed to the investigational product;

- A male has been exposed (eg, because of environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form and the Exposure During Pregnancy Supplemental form, as applicable, regardless of whether there is an associated SAE. In the event of an EDP, the information submitted should include the anticipated date of delivery. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the ISF.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs are as follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form.

8.3.6. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of administering the investigational product. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in Appendix 4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 2 of the protocol.

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8.3.6.1. Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device incidents is provided in Appendix 4.

8.3.6.2. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

Refer to the IP manual for instructions on reporting medical device incidents.

The same individual will be the contact for the receipt of medical device reports and SAEs.

8.3.6.4. Regulatory Reporting Requirements for Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/EC.

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8.3.7. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration by an incorrect route;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

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8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 0.5 mL will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

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

No interruptions or dose modifications will be made in this study.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics will be evaluated in exploratory analyses assessing vaccine impact on healthcare resource utilization parameters evaluated during study visits, 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.

8.10. Procedures – Maternal Participants

8.10.1. Screening and Vaccination Visit (Clinic; Day -28 to Day 1 – Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory.

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Maternal participants who might be illiterate must thumbprint the ICD and it must be signed and dated by an impartial witness who was present throughout the entire informed consent process before performing any study-related procedures.

The investigator or his or her designee will also sign and date the ICD. A copy of the signed/thumbprinted and dated ICD must be given to the maternal participant. **The source data must reflect that the informed consent was obtained before participation in the study.**

If the maternal participant is found ineligible for the study based on a full assessment of inclusion and exclusion criteria, the investigator may advise the participant, either by telephone or face to face, that the participant will be excluded from further participation in the study, as defined in Section 5.4. **All eligible maternal participants will proceed to complete the vaccination visit.**

Standard-of-care procedures performed **prior to informed consent** can be considered for use in the study provided they are performed in close proximity (*approximately 28 days)* to the timing of vaccination and follow guidance around the timing of procedures stipulated in the protocol.

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

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

The following procedures will be performed:

- Obtain written informed consent from the maternal participant before performing any study-specific procedures. If the maternal participant is illiterate, she must thumbprint the ICD and it must be signed and dated by an impartial witness who was present throughout the entire informed consent process.
- Assign a single participant identifier using the IRT system.
- Obtain and record the participant demography (including complete date of birth [dd-Mmm-YYYY], sex, race, and ethnicity). The date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record current alcohol, tobacco, marijuana, or any illicit drug usage.
- Obtain and record any medical, surgical, and obstetric history of clinical significance including history from prior and current pregnancy(ies). Refer to the ISF for further details.

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- Record the LMP and estimated delivery date (EDD).
- Measure and record vital signs, including oral temperature, seated blood pressure, and heart rate.
- Record in the source documentation the weight and height at first obstetric visit during current pregnancy and date of measurements.
- Perform targeted physical examination evaluating/noting any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Significant medical and surgical history and abnormal observations from the physical examination will be documented and recorded in the CRF.
- Perform obstetric examination including but not limited to fetal heart tones and fetal movement.
    - Where an obstetric ultrasound examination is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination.
    - Note: Physical or obstetric examinations performed as standard of care may be admissible if performed **within 10 days** prior to the vaccination visit.
- Obtain details of any Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given at any time during the current pregnancy.
- Obtain details of any nonstudy vaccinations given at any time during the current pregnancy.
- Obtain details of syphilis, HIV, and HBV status.
    - Note: Only participants with a documented negative syphilis test result and negative HIV antibody and HBV surface antigen test results obtained during the current pregnancy are eligible for randomization.
    - If not performed as standard of care, assessment should be performed as part of the study, locally, and vaccination of maternal participant should be deferred until the results are available and confirmed to be negative within 28 days prior to study randomization.
- **Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.**
- Ensure that the maternal participant meets none of the temporary delay criteria as described in Section 5.2.3.

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- Issue the maternal participant an e-diary and provide instructions on its completion.
- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures, and provide instructions on their use.
- Obtain and record baseline assessment of systemic events prior to vaccination in the maternal participant's source documents. Ask the maternal participant to capture the corresponding baseline systemic event measurements in her e-diary.
- Prior to vaccination, collect a blood sample of approximately 15 mL for serologic assessments.
- Obtain the maternal participant's randomization number and investigational product kit number using the IRT system. Refer to the IRT manual for further instructions on this process.
- Qualified site staff member(s) will administer a single 0.5-mL dose of investigational product into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IP manual for further instruction on this procedure.
- Site staff must observe the maternal participant for any acute reactions for at least 30 minutes after investigational product administration.
- Record any acute reactions in the maternal participant's source documents, on the AE page of the CRF, and on an SAE form as applicable.
- Ask the maternal participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, **OR** explain to the maternal participant that a field worker will visit her every day from Day 2 to Day 7 after vaccination (where Day 1 is the day of vaccination) to take her temperature and record systemic events, acute local reactions, and use of antipyretic medication in a diary (if applicable).
- Ask the maternal participant to contact the site staff or investigator immediately if she experiences any of the following from Day 1 to Day 7 after vaccination to determine if an unscheduled reactogenicity visit is required as detailed in Section 8.10.5 **OR** inform the maternal participant that if she experiences any of the following from Day 1 to Day 7 after vaccination or is taking antipyretic medication at Day 7, then the field worker will continue to visit until resolution. Furthermore, the maternal participant will be referred to the appropriate healthcare facility at the discretion of a field worker if there are any concerns as detailed in Section 8.10.5.
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring >20 measuring device units (greater than 10 cm).

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- Severe pain at the injection site.
- Any severe systemic event.
- Any blackening of the skin (necrosis) at the injection site.
- Any peeling/scaling of the skin (exfoliative dermatitis).

- Inform the maternal participants that if a temperature of ≥100.4°F (≥38.0°C) is recorded during the collection of diary data, she will be required to have a rapid test for malaria as per local practice and details will be recorded in the diary (if applicable, based on local practice).
- Remind maternal participants that study staff may contact them to obtain additional information on events entered into the e-diary.
- Remind maternal participants to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in Section 8.2 and Section 10.2.
- Remind the maternal participant to bring the completed e-diary to the next visit *(if applicable*).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and the blinded dispenser/administrator completes the investigational product accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.
- Maternal participants will be instructed to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.
- Request the maternal participant to contact the site if she goes into labor/is admitted to the maternal unit (*The field worker will contact the maternal participant prior to the next study visit to remind her, if applicable*).

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8.10.2. 1-Month Follow-up Visit (Clinic or Telephone; 28 to 42 Days After Vaccination)

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

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.2.
- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Record details of any MA-RTI, including if the MA-RTI is infectious or noninfectious, location details (upper or lower RTI), and prescribed medications since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Complete the maternal participant's source documents.
- Record AEs and SAEs as described in Section 8.2 and Section 10.2. Note: Active elicitation and collection of AEs and SAEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination.
- The investigator or an authorized designee completes the CRF.
- Maternal participants will be instructed to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.
- Request the maternal participant to contact the site if she goes into labor/is admitted to the maternal unit (*The field worker will contact the maternal participant prior to the next study visit to remind her, if applicable*).

8.10.3. Delivery (Maternity Unit)

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

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.2.
- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given since the last visit.

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- If available, record the maternal participant's GBS status and if any medication was given for IAP.

- Record details of any nonstudy vaccinations given since the last visit.

- Collect a blood sample of approximately 15 mL for serologic assessments. Note: The maternal participant's blood sample can be taken at any time during the delivery visit, **preferably before 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. Refer to the ISF for blood sample collection guidelines.

  Note: A cord blood sample of approximately 10 mL for immunogenicity assessments must also be collected. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord and after the umbilical cord has been clamped and cut. This sample should be labeled with the **infant's participant ID number.**

- Record pregnancy outcome information including vital status of the infant (live, stillbirth, spontaneous abortion, or miscarriage), mode of delivery (vaginal delivery, cesarean section, etc), and the use of any assisted devices (forceps or vacuum).

- Record details of any MA-RTI associated with a medical visit, including if the MA-RTI is infectious or noninfectious, location details (upper or lower RTI), and prescribed medications since the last visit.

- Record AEs as described in Section 8.2 and Section 10.2.

- Ask the maternal participants to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.

- Ask the maternal participant to contact the site staff or investigator if her newborn infant meets the MA-RTI assessment criteria OR the field worker will contact the maternal participant/legal guardian(s) weekly to remind them to report any MA-RTI (*if applicable*).

- Complete the participant's source documents.

- The investigator or an authorized designee completes the CRF.

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8.10.4. 6-Month-Postdelivery Visit (Clinic or Telephone; 180 to 210 Days After Delivery)

- Obtain details of any postnatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [eg, HBIG]) or Rho(D) immune globulin [eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Record details of any MA-RTI, including if the MA-RTI is infectious or noninfectious, location details (upper or lower RTI), and prescribed medications since the last visit.
- Ask the maternal participant to contact the site staff or investigator if her infant meets the MA-RTI assessment criteria OR the field worker will contact the maternal participant/legal guardian(s) weekly to remind them to report any MA-RTI, if applicable.
- Record AEs as described in Section 8.2 and Section 10.2.
- Complete the maternal participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.5. Unscheduled Reactogenicity Visits

If the maternal participant reports 1 or more of the following, a contact **must** occur as soon as possible between the maternal participant and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled reactogenicity visit is required **OR** based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the field worker if there are any concerns regarding reactogenicity events, including:

- redness at the injection site on the arm in which the investigational product was administered measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site on the arm in which the investigational product was administered measuring >20 measuring device units (>10.0 cm),
- severe injection site pain on the arm that the investigational product was administered,
- fever ≥39.0°C (≥102.1°F).

A site visit or referral to a healthcare facility should be scheduled as soon as possible to assess the extent of the reaction, unless:

- The maternal participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or

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- The participant/field worker recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator or appropriate designee determines that the visit is not required.

This contact will be recorded in the maternal participant's source notes and in the CRF.

Any ongoing reactions must be assessed at the next scheduled visit.

The reactogenicity events should be assessed by the investigator or a medically qualified member of the site staff such as a study physician or a study nurse, as applicable to the investigator's local practice or healthcare facility, who will:

- Measure oral temperature.
- Measure the participant's heart rate.
- Measure the participant's blood pressure (seated).
- Measure the minimum and maximum diameters of redness (if present) on the arm in which the investigational product was administered.
- Measure the minimum and maximum diameters of swelling (if present) on the arm in which the investigational product was administered.
- Assess if necrosis is present at the injection site on the arm in which the investigational product was administered.
- Assess if any exfoliative dermatitis is present.
- Assess any injection site pain on the arm in which the investigational product was administered that is present in accordance with the reactogenicity grading scale provided in Section 8.2.1.1.
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 8.2.1.2.
- Ask the participant if she attended an emergency room visit or was hospitalized.
- For severe pain at the injection site resulting in an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, any necrosis on the arm in which the investigational product was administered, or exfoliative dermatitis, the investigator or qualified designee must assess these events in accordance with the intensity AE grading scale provided in Section 8.2.1.1 and Section 8.2.1.2.

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- Record AEs and SAEs as described in Section 8.2 and Section 10.2.
- Complete the participant's source documents.
- The investigator or an authorized designee will complete the CRFs.

The study staff/field worker may contact the participant to obtain additional information on events entered into the e-diary, as appropriate.

8.10.6. RTI Surveillance Procedures and Telephone Contact Criteria – Maternal Participants

- Starting from Day 1 after vaccination (where Day 1 is the day of vaccination) until the end of the study, all maternal participants will be monitored for MA-RTIs as detailed in Section 1.2.3.1 and Section 8.1.2. Maternal participants should notify the site and/field worker of the occurrence of any MA-RTIs immediately but no later than the next study visit. Note: Site contact may be by an electronic method of communication (including but not limited to electronic messaging, short message service [SMS], text, email), by phone call, or by face-to-face contact.
- The definition of maternal RTI includes 1 or more of the following signs and/or 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
- Record the details of any MA-RTI, including the medically attended visit location (hospital, outpatient visit, emergency room, urgent care, or home visit), duration of hospitalization, intensive care unit (ICU) duration if applicable, prescribed medications for the MA-RTI, assessments including RSV test result (eg, NAAT, rapid antigen detection tests, or any other molecular diagnostic test), if available, and the final diagnosis.
- Based on the diagnosis provided, the investigator should denote whether the medically attended respiratory illness was infectious or noninfectious, and comprised the upper and/or lower airways.

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- Record the details of any nonstudy vaccinations.
- Record AEs as described in Section 8.2 and Section 10.2. *Note: MA-RTIs are study endpoints and should not be reported as AEs.*
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.11. Procedures – Infant Participants

8.11.1. Infant Participants: Visit 1 – Birth (Hospital, Birth to 7 Days After Birth)

- Manually assign a single infant participant identifier using the IRT system (or equivalent).
- Collect a cord blood sample of approximately 10 mL for immunogenicity assessments. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord and after the umbilical cord has been clamped and cut. This sample should be labeled with the **infant's participant ID number**.
- If cord blood is unavailable, a blood sample may be collected from the infant participant preferably within 24 hours, but up to 7 days after birth. The volume of blood collected will be based on the weight of the infant (refer to Table 4).
- Ensure and document that all the infant inclusion criteria and none of the infant exclusion criteria are met.
- Collect demography (including complete date of birth [ie, dd-Mmm-YYYY], sex, race, and ethnicity). The date of birth will be collected to critically evaluate the immune response.
    - Obtain and record the infant's length, head circumference, and weight at birth. *Note: Birth weight must be the first birth weight and cannot be based on the standard-of-care examination.*
    - Obtain and record the infant's birth data, including GA and appearance, pulse, grimace, activity, and respiration (Apgar) score.
    - Obtain and record background factors as described in Section 10.5.
    - Measure vital signs, including rectal temperature, heart rate, oxygen saturation by pulse oximetry, and respiratory rate.
    - Standard-of-care physical examination procedures can be considered for use in the study provided they were performed within 48 hours after birth. Note: Please reference the physical examination procedures below for details.

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

    - Record details of any major congenital anomalies on the AE page of the CRF, and report as an SAE as described in Section 10.2.3.

- Record any medication as described in Section 6.5.5.

- Obtain details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given to the infant participant since birth.

- Record AEs as described in Section 8.3 and Section 10.2.

- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.

- Review the weekly contact schedule with the parent(s)/legal guardian(s) and collect contact information **OR** remind the parent(s)/legal guardian(s) that a field worker will contact them weekly to remind them to report any MA-RTI (if applicable).

- Ask the parent(s)/legal guardian(s) to contact the investigator or qualified designee immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI visit criteria. An MA-RTI assessment visit along with collection of a nasal swab must be performed for all MA-RTIs as described in Section 1.2.4.1 and Section 8.11.7.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

8.11.2. Visit 2 – 1-Month Follow-up (Clinic, 28 to 48 Days After Birth)

- Obtain and record background factors as described in Section 10.5.

- Obtain and record the infant's length, head circumference, and weight.

- Measure vital signs, including temperature, heart rate, oxygen saturation by pulse oximetry, and respiratory rate.

- Standard-of-care physical examination procedures can be considered for use at this study visit, if they were performed 14 days prior to this visit. Note: Please reference the physical examination procedures below for reporting details.

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- Perform a targeted physical examination, if not performed as part of standard of care, noting any clinically significant abnormalities. Newly identified abnormal findings must be recorded on source documents and the physical examination page and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF.
    - Record details of any newly emergent major congenital anomalies on the AE page of the CRF, and report as an SAE as described in Section 10.2.3.
- Record details of any NDCMCs.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.2.
- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.
- Ask the parent(s)/legal guardian(s) to contact the investigator or qualified designee immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI assessment criteria. An MA-RTI assessment visit along with collection of a nasal swab must be performed for all MA-RTIs as described in Section 1.2.4.1 and Section 8.11.7.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.
- Contact the infant participant's parent(s)/legal guardian(s) approximately every 7 days from birth until the 6-month follow-up visit to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the RTI medical visit criteria. The weekly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.7.1 for guidance on reported cases of MA-RTIs in infant participants during the first 6 months after birth.

8.11.3. Visit 3 – 6-Month Follow-up Visit (Clinic, 180 to 210 Days After Birth)

- Obtain and record background factors as described in Section 10.5.
- Obtain and record the infant's length, head circumference, and weight.
- Standard-of-care physical examination procedures can be considered for use at this study visit, if they were performed 14 days prior to this visit. Note: Please reference the physical examination procedures below for reporting details.

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- Perform a targeted physical examination, if not performed as part of standard of care, noting any clinically significant abnormalities. Newly identified abnormal findings must be recorded on source documents and the physical examination page and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF.
    - Record details of any newly emergent major congenital anomalies on the AE page of the CRF, and report as an SAE as described in Section 10.2.3.
- Record details of any NDCMCs.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.2.
- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.
- Contact the infant participant's parent(s)/legal guardian(s) approximately every month (28 to 35 days) until the end-of-study visit, to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the MA-RTI assessment criteria. The monthly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.8 for guidance on reported cases of MA-RTIs in infant participants.
- Ask the parent(s)/legal guardian(s) to contact the investigator immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI assessment criteria. **An MA-RTI assessment visit along with a nasal swab must be performed for all hospitalizations due to an RTI and severe MA-LRTIs as described in Section 1.2.4.1 and Section 8.11.8.**

8.11.4. Visit 4 – 12-Month Follow-up (Clinic or Telephone; 350 to 378 Days After Birth)

- Obtain and record background factors as described in Section 10.5.
- Obtain and record the infant's length, head circumference, and weight *(only applicable if a clinic visit is conducted).*
- Standard-of-care physical examination procedures can be considered for use at this study visit, if they were performed 14 days prior to this visit. Note: Please reference the physical examination procedures below for details.

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- Perform a targeted physical examination, if not performed as part of routine care *as described above*, noting any clinically significant abnormalities. Newly identified abnormal findings must be recorded on source documents and the physical examination page and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF. *Only applicable if a clinic visit is conducted.*

- Obtain and record details of any NDCMCs or newly emergent major congenital anomalies.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record AEs as described in Section 8.3 and Section 10.2.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the end-of-study CRF for all infant participants except for infant participants born during the first year of the study.

- The investigator or an authorized designee completes the CRF for infant participants born during the first year of the study. *Note: An additional 12-month blinded follow-up period for longer-term RTI surveillance and safety oversight will be included for these participants.*

- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.

- Confirm the understanding of the infant participant's parent(s)/legal guardian(s) regarding site contact for the study, which is approximately every month (28 to 35 days) until the end-of-study visit. Ask the parent(s)/legal guardian(s) to contact the investigational site/field worker promptly if the infant meets the MA-RTI assessment criteria. The monthly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.8 for guidance on reported cases of MA-RTIs in infant participants.

- *Infant participants born during the first year of the study only*: Ask the parent(s)/legal guardian(s) to contact the investigator immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI assessment criteria.
  An MA-RTI visit along with collection of a nasal swab must be performed for all hospitalizations due to an RTI and severe MA-LRTIs as described in Section 1.2.4.1 and Section 8.11.8.

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8.11.5. Visit 5 – 18-Month Follow-up Visit (Telephone; 525 to 574 Days After Birth; Infant Participants Born During the First Year of the Study Only)

- Obtain and record background factors as described in Section 10.5.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Obtain and record details of any NDCMCs or newly emergent major congenital anomalies.
- Record AEs as described in Section 8.3 and Section 10.2.
- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.
- Contact the infant participant's parent(s)/legal guardian(s) approximately every month (28 to 35 days) until the end-of-study visit, to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the MA-RTI assessment criteria. The monthly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.8 for guidance on reported cases of MA-RTIs in infant participants.
- Infant participants born during the first year of the study only: Ask the parent(s)/legal guardian(s) to contact the investigator immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI assessment criteria**.**
  An MA-RTI assessment visit along with collection of a nasal swab must be performed for all hospitalizations due to an RTI and severe MA-LRTIs as described in Section 1.2.4.1 and Section 8.11.8.

8.11.6. Visit 6 – 24-Month Follow-up Visit (Clinic or Telephone; 714 to 742 Days After Birth; Infant Participants Born During the First Year of the Study)

- Obtain and record background factors as described in Section 10.5.
- Obtain and record the infant's length, head circumference, and weight *(only applicable if a clinic visit is conducted).*
- Standard-of-care physical examination procedures can be considered for use at this study visit, if they were performed 14 days prior to this visit. Note: Please reference the physical examination procedures below for reporting details.

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- Perform a targeted physical examination, if not performed as part of routine care, noting any clinically significant abnormalities. Newly identified abnormal findings must be recorded on source documents and the physical examination page and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF. *Only applicable if a clinic visit is conducted.*

- Obtain and record details of any NDCMCs or newly emergent major congenital anomalies.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record AEs as described in Section 8.3 and Section 10.2.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the end-of-study CRF for all infant participants born during the first year of the study.

8.11.7. Active RSV Surveillance Procedures and Visit Criteria (Birth to 6 Months After Delivery)

- This is an active surveillance period spanning from birth through 6 months after delivery (Visit 3).

- The sponsor may alter the frequency of the weekly contacts or the duration of surveillance for MA-RTI based on RSV surveillance data or other operational factors.

8.11.7.1. RTI Associated With a Medical Visit – Hospital, Home, or Clinic Visit

- Contact the infant participant's parent(s)/legal guardian(s) approximately every week (7 to 10 days) from birth until Visit 3 (6-month follow-up visit), to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the criteria for an RTI-associated medical visit. The weekly contact may be via the e-diary device or study-related mobile application, text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Table 1 regarding clinical signs and symptoms that meet the study definition of an MA-RTI, and Section 1.2.4.1 for study-required assessments.

- Note: If the parent(s)/legal guardian(s) reports to the investigational site staff that the infant has experienced an event requiring a visit to a healthcare provider, the site staff and/field worker should confirm, based on information provided, whether the event meets the criteria for an MA-RTI. Please refer to Table 1 and Section 8.1 regarding clinical signs and symptoms that meet the study definition of an MA-RTI, and Section 1.2.4.1 for study-required assessments.

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- When an infant MA-RTI criterion is met or confirmed, the site/field worker will obtain records from the medically attended visit and record the healthcare information as detailed in Appendix 6.

- When an infant MA-RTI criterion is met or confirmed, the **infant participant** will be seen as soon as possible and **within 72 hours** of site/field worker awareness for assessment by the investigational site staff or qualified designee.

- The infant participant may be seen either at the time of the MA-RTI, at home or at the study site (if discharged), or if the infant participant has been hospitalized or is receiving treatment at another medical facility, the site staff/field worker can conduct the visit at those facilities.

    - If a study visit is not performed within 72 hours of site/field worker awareness, it should still be performed, including the collection of nasal swab specimens.

    - Targeted assessments at an MA-RTI assessment visit include but are not limited to:

        - **Respiratory signs:** apnea (observed only) or lower chest wall indrawing.

        - **Vital sign assessment:** respiratory rate, heart rate, and oxygen saturation by pulse oximetry.

- Nasal swab collection from the infant participant for testing at the central laboratory.

- Obtain and record background factors as described in Section 10.5.

- Obtain and record details of the RTI event, including office visits, urgent care, and emergency room or hospitalization details, including the date and time of the visit. Record the following in the CRF based on the site records:

    - **Respiratory signs:** apnea (noted to be observed only) or lower chest wall indrawing.

    - **Vital sign assessment:** respiratory rate, heart rate, and oxygen saturation by pulse oximetry.

    - **Note:** record the values that represent the worst day of illness.

- Record any medication as described in Section 6.5.5.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record AEs as described in Section 8.3 and Section 10.2. *Note: MA-RTIs are study endpoints and should not be reported as AEs.*

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- Request that the parent(s)/legal guardian(s) contact the site/field worker if the infant's illness worsens, or if the infant is hospitalized.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

- Compile the adjudication submission package for the event as detailed in Section 8.1.

8.11.8. Long-Term RSV and Safety Surveillance Procedures and Visit Criteria

- *This is a long-term surveillance procedure for all infant participants from 6 months after delivery (Visit 3) until the last study visit.*

- Contact the infant participant's parent(s)/legal guardian(s) approximately every month (28 to 35 days) from Visit 3 (6-month follow-up visit) until the end-of-study visit, to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the criteria for an MA-RTI visit. The monthly contact may be via the e-diary device or study-related mobile application, text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.1 regarding clinical signs and symptoms that meet the study definition of an MA-RTI, and Section 1.2.4.1 for study-required assessments.

- Note: If the parent(s)/legal guardian(s) reports to the investigational site staff that the infant has experienced an MA-RTI, the site should obtain additional information and determine whether the event also meets the study definition of a severe MA-LRTI.

    - **Note:** Severe MA-LRTI is defined in Table 1.

- The site/field worker will obtain records from the medically attended visit and record the healthcare information as detailed in Appendix 6.

- When an infant MA-RTI criterion is confirmed and also meets the study definition of hospitalization due to an RTI or a severe MA-LRTI, the **infant participant** will be seen as soon as possible and **within 72 hours** of site/field worker awareness for nasal swab collection by the investigational site staff/field worker. The staff/field worker will obtain the nasal swab **within 72 hours** of awareness with the infant participant either at home (if discharged) or, if the infant participant has been hospitalized or receiving treatment at another medical facility, the site staff/field worker will conduct the visit at those facilities.

    - **Note:** Nasal swab collection from the infant participant is for testing at the central laboratory.

- Targeted assessments will be required for all reported cases of hospitalization due to an RTI or severe MA-LRTI only, and this includes but is not limited to:

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- **Respiratory signs**: apnea, lower chest wall indrawing.
- **Vital sign assessment:** respiratory rate, heart rate, and oxygen saturation by pulse oximetry.

- A targeted assessment visit is not required for an MA-RTI event not meeting the definition of hospitalization due to an RTI or severe MA-LRTI.
- Obtain and record background factors as described in Section 10.5.
- Obtain and record details of the MA-RTI event, including emergency room or hospitalization details with admission and discharge date (if applicable).
- Record any medication as described in Section 6.5.5.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.2. *Note: MA-RTIs are study endpoints and should not be reported as AEs.*
- Request that the parent(s)/legal guardian(s) contact the site if the infant's illness worsens, or if the infant is hospitalized.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.
- Compile the adjudication submission package for hospitalizations due to an RTI and severe MA-LRTI events only as detailed in Section 8.1.

8.12. Communication and Use of Technology

In a study of this duration that is event-driven, it is vital to ensure that communication between the study site and the maternal participant and parent(s)/legal guardian(s) is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant (maternal and/or infant participant), to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, a communication pathway between the maternal participant and parent(s)/legal guardian(s) and the study site staff will be established. The maternal participant and the parent(s)/legal guardian(s) may be able to utilize their own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

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- Contact with the investigator.
- The ability of the maternal participant/parent(s)/legal guardian(s) to report MA-RTI visits associated with the infant participant.
- An alert in the event that the maternal or infant participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (e-diary).

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

The null hypothesis to be tested concerns VE for the primary endpoint. The RSV vaccine will be compared to placebo, testing the hypotheses H_0: VE ≤20% vs H_a: VE >20%. For all secondary efficacy endpoints, the RSV vaccine will be compared to placebo, testing the hypotheses H_0: VE ≤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.

9.1.1. Estimands – Infant Participants

9.1.1.1. Efficacy

In infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants):

- VE, defined as the percentage relative risk reduction in the incidence of MA-LRTI due to RSV in the RSV vaccine group, relative to the placebo group;
- VE, defined as the percentage relative risk reduction in the incidence of severe MA-LRTI due to RSV in the RSV vaccine group, relative to the placebo group;
- VE, defined as the percentage relative risk reduction in the incidence of hospitalization due to RSV in the RSV vaccine group, relative to the placebo group;
- VE, defined as the percentage relative risk reduction in the incidence of all-cause MA-LRTI in the RSV vaccine group, relative to the placebo group.

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These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.1.2. Immunogenicity

In infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants):

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

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.1.3. Safety

In infant participants born to the maternal participants receiving 1 dose of investigational product:

- The percentage of infant participants with specific birth outcomes.
- The percentage of infant participants having AEs from birth through 1 month of age.
- The percentage of infant participants having SAEs, NDCMCs, and new diagnosed congenital anomalies from birth through the last study visit.

Missing AE dates and missing AE intensity will be handled according to Pfizer safety rules.

9.1.2. Estimands – Maternal Participants

9.1.2.1. Immunogenicity

In maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants):

- The immune response, estimated by the GMT for RSV A and RSV B 50% neutralizing antibody titers.
- The immune response, estimated by the GMFR from baseline in RSV A and RSV B 50% neutralizing antibody titers.

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- GMR, estimated by the ratio of the GMTs for RSV A and RSV B 50% neutralizing antibody titers of the RSV vaccine group to the placebo group.
- Geometric mean of the IgG levels against RSV prefusion F.
- Geometric mean of the Ig levels to nonvaccine RSV antigens.

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.2.2. Safety

In maternal participants receiving 1 dose of investigational product:

- The percentage of maternal participants reporting AEs through 1 month after vaccination.
- The percentage of maternal participants reporting obstetric complications and SAEs through the end of the study.
- The percentage of maternal participants reporting local reactions within 7 days of vaccination, in the subset of participants completing e-diaries.
- The percentage of maternal participants reporting systemic events within 7 days of vaccination, in the subset of participants completing e-diaries.

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

9.2. Sample Size Determination

This is a case-driven study. Sample size is determined as the number of participants to be randomized that is expected to accrue the required number of primary endpoint cases in the evaluable population. In this study there are 2 primary endpoints, and success on either primary endpoint is sufficient (see Section 9.1); power for the study overall is therefore at least as high as the power for either primary endpoint individually. In order for the study to have at least 90% power to reject the null hypothesis for MA-LRTI due to RSV when true VE is 60%, a total of 124 cases of MA-LRTI due to RSV within 90 days of birth are required in the evaluable population. This also accounts for potential use of a nominal alpha of 1.25% 1-sided within the Hochberg multiplicity adjustment. There is no explicit case target for the endpoint of severe MA-LRTI due to RSV; depending on the assumed true VE, power for that individual hypothesis may be lower, but the power for the primary endpoint family will be at least 90%. Hypotheses about VE may be restated as hypotheses about the proportion of cases in the RSV vaccine group, conditional upon a fixed total number of cases. If this proportion is p, the null hypothesis H_0: VE ≤20% is equivalent to H_0: $p \geq 0.444$; the assumption of VE = 60% corresponds to $p = 0.286$. Power was evaluated by the exact

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binomial test, and the case target established as that number k for which power is guaranteed to be at least 90%, for all $k^* \geq k$. The calculation accounted for the study design (1:1 randomization of participants to RSV vaccine : placebo), a single planned interim analysis of efficacy (see Section 9.5), and an overall type 1 error of 2.5% 1-sided across the 2 primary endpoints.

This global study is planned to be conducted in the United States and other high-income countries as well as LMICs. Incidence rates of the primary endpoints are expected to vary in different regions. Based on a recently completed Phase 3 trial of an RSV vaccine, the assumed incidence rate for MA-LRTI due to RSV through 90 days in low-incidence countries, such as the United States, is approximately 1.75%; and in other regions, approximately 3.90%. With these assumptions, and also allowing for 60% VE and 10% of enrolled participants being nonevaluable, enrollment of approximately 6900 participants is planned for the study as a whole. The exact number of participants required to accrue the case target may be higher or lower than this, depending on incidence rates, observed VE, and the proportion of participants evaluable.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined for infant and maternal participants:

Population	**Description**
Enrolled	All maternal participants who sign the ICD.
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 eligible, are born to the maternal participants who received the investigational product to which they were randomized at least 14 days prior to delivery, have valid and determinate results for the proposed analysis, and have no major protocol violations.
Modified intent-to-treat (mITT) efficacy – infant	All infant participants who are born to vaccinated maternal participants and have valid and determinate results for the proposed analysis.
Evaluable immunogenicity – infant	All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
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, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.

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Population	Description
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.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for the first planned analysis and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	• The analysis of efficacy will use 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. The incidence of MA-LRTI due to RSV and severe MA-LRTI due to RSV in infant participants will be evaluated in both groups up to 90 days, 120 days, 150 days, and 180 days after birth. • The infant evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the infant mITT efficacy population. • The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV will be tested in parallel using a Hochberg multiplicity adjustment procedure. Success of the trial requires rejection of the null hypothesis (ie, a CI lower bound >20%) for either one of the 2 primary endpoints. • The primary endpoint of severe MA-LRTI due to RSV may be demoted to a secondary endpoint, if there are insufficient cases for an adequately powered analysis. During the trial, blinded accrual of cases will be monitored and prior to any unblinding, a decision rule for this change will be established based on the total number of cases of severe MA-LRTI due

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	to RSV. • Testing of each of the primary endpoints will follow a fixed sequence. First, the hypothesis pertaining to the incidence within 90 days after birth will be tested, at the full nominal alpha level. If that null hypothesis cannot be rejected, testing for that endpoint ends. Otherwise, testing proceeds to the incidence within 120 days after birth, at the full nominal alpha level. In the same way, 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. • There may be a single interim analysis of the primary endpoint when there is an adequate number of cases (at least half the target number within 90 days). Based on the fraction of cases included in the interim analysis, a nominal alpha level will be derived based on a Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. For example, if there is a single interim analysis at exactly 50% of the cases, the appropriate nominal 1-sided significance levels are 0.0014 at the interim analysis and 0.0245 at the final analysis. Implementation of these nominal 1-sided significance levels ensures the overall type 1 error for the primary endpoint will be no more than 0.025. See Section 9.5 for more details. • At the interim analysis there will also be an assessment for futility, based on conditional power for the primary endpoint. If the probability of success at the end of the trial is low, given the interim analysis results and the initially assumed VE is applied to the remaining data, consideration will be given to stopping the study for futility. • CIs for VE will be calculated using the nominal alpha level α. If the lower 100(1 - α)% confidence limit for VE exceeds 20%, the null hypothesis will be rejected. • At the end of the trial, the RSV vaccine may be deemed efficacious if there are 43 or fewer cases of MA-LRTI due to RSV in the RSV vaccine group out of the 124 total primary endpoint cases. This corresponds to estimated VE = 47% with 95.1% CI = (22%, 64%). For severe MA-LRTI, assuming a total of 50 cases occur, the vaccine may be deemed efficacious if there are 14 or fewer cases in the RSV vaccine group. This corresponds to estimated VE = 61% with 95.1% CI = (26%, 81%). • Kaplan-Meier curves showing accrual of primary endpoint cases over 180 days will be presented.

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Secondary	• The analysis of secondary efficacy endpoints will use the exact conditional binomial method, as for the primary endpoint. Secondary endpoints will be examined at the final analysis only. VE will be estimated along with 2-sided 95% CI. • Inference for the secondary endpoints will be conditional upon demonstrating success for the primary efficacy endpoint. The secondary endpoints of hospitalizations due to RSV and all-cause MA-LRTI will be tested in parallel so as to preserve the overall type 1 error across primary and secondary endpoint families at no more than 2.5% 1-sided. Multiplicity correction strategies will be defined in the SAP. VE for each secondary endpoint will be evaluated sequentially at 90 days, 120 days, 150 days, and 180 days, as for the primary endpoint. Testing will only proceed to later time points conditional on success of all previous time points. • The infant evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the infant mITT efficacy population.
Exploratory	• The incidence in infant participants of MA-RTIs due to RSV with protocol-defined criteria occurring within 730 days after birth will be summarized. • The incidence in infant participants of MA-RTIs due to any cause with protocol-defined criteria occurring within 730 days after birth will be summarized. All MA-RTIs and severe MA-LRTIs will be summarized separately. • The primary endpoint through 181 days after birth will be summarized separately as cases associated with RSV subgroup A or RSV subgroup B infection. • The primary endpoint through 181 days after birth will be summarized by interval from vaccination to delivery and by GA at the time of vaccination. • The incidence of MA-RTI due to any cause in maternal participants from vaccination through 180 days after delivery will be summarized. Outcomes to be summarized will include all-cause MA-RTI, all-cause medically attended upper RTI, and all-cause MA-LRTI. • Variations on the primary and secondary endpoint definitions to include RSV positives from non–NAAT-based testing will be explored and summarized descriptively.

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9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	• The point estimate and exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event for each vaccine group. • A 3-tier approach will be used to summarize AEs. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in the percentage of participants reporting the events between the RSV vaccine group and the placebo group will be calculated using the test statistic proposed by Miettinen and Nurminen; in addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. A Medical Dictionary for Regulatory Activities (MedDRA) preferred term is defined as a Tier 2 event if there are 1% or more participants in at least 1 vaccine group reporting the event. • The safety analyses are based on the safety population. Participants will be summarized by the vaccine group corresponding to the vaccine they (for maternal participants) or their mothers (for infant participants) actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE intensity will be addressed using the Pfizer safety rules.
Secondary	• The point estimate and exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by the vaccine group corresponding to the vaccine they (for maternal participants) or their mothers (for infant participants) actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE intensity will be addressed using the Pfizer safety rules.
Exploratory	• These analyses will be described in the SAP, finalized before first database lock.

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9.4.3. Other Analyses

9.4.3.1. Immunogenicity Analyses

Immunogenicity endpoints are exploratory in the study. The analyses of immunogenicity endpoints will be based on the evaluable populations. An additional analysis will be performed based on the mITT populations if there is enough difference between the mITT populations and the evaluable populations. Immunogenicity data for maternal participants and infant participants will be summarized separately, with the exception of maternal-to-infant placental transfer analysis. Participants will be summarized according to the vaccine group to which they (for maternal participants) or their mothers (for infant participants) were randomized.

The secondary and exploratory immunogenicity endpoints will be described by the following summaries and the 95% CIs:

- GMT of the RSV A– and RSV B–neutralizing antibody titers at each available time point by vaccine group (maternal participants and infant participants, separately).
- GMT of the combined RSV A/B–neutralizing antibody titer, defined as the geometric mean of the RSV A– and RSV B–neutralizing antibody titers, at each available time point by vaccine group (maternal participants and infant participants, separately).
- GMFR for RSV A– and RSV B–neutralizing antibody titers from before vaccination to each available time point after vaccination by vaccine group (maternal participants only).
- GMFR of the combined RSV A/B–neutralizing antibody titer, defined as the geometric mean of the RSV A– and RSV B–neutralizing antibody titers, from before vaccination to each available time point after vaccination by vaccine group (maternal participants only).
- GMR of the RSV vaccine group to the placebo group for the RSV A– and RSV B–neutralizing antibody titers at each available time point after vaccination (maternal participants and infant participants, separately).
- GMR of the RSV vaccine group to the placebo group for the combined RSV A/B–neutralizing antibody titers at each available time point after vaccination (maternal participants and infant participants, separately).
- Geometric mean of the IgG levels against RSV prefusion F and Ig levels to nonvaccine RSV antigens at each available time point by vaccine group (maternal participants and infant participants, separately).
- Geometric mean of IgG subclass levels (minimally IgG1) against RSV prefusion F at each available time point by vaccine group (maternal participants only).

Empirical reverse cumulative distribution curves (RCDCs) for combinations of time points and vaccine groups will be presented for RSV A– and RSV B–neutralizing antibody titers.

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A sensitivity analysis will be performed to exclude immunogenicity data from mothers and their infants following onset of RSV infection between vaccination and delivery (based on evidence from the nonvaccine antigen assay).

Subgroup analyses of the secondary and exploratory immunogenicity endpoints will be performed, including an analysis based on GA at the time of vaccination, time from vaccination to delivery, and by country subcategories. All subgroup analyses will be defined in the SAP.

In addition, the maternal-to-infant placental transfer ratio (infant/mother) of RSV A– and RSV B–neutralizing antibody titers and associated 95% CI will be summarized.

9.4.3.2. Healthcare Utilization Analyses

Healthcare utilization endpoints are exploratory in the study; these analyses will be described in the SAP and finalized before first database lock. For these analyses, details of healthcare resource utilization for all infants will be assessed at each MA-RTI visit from birth through the last study visit (730 days after birth). Details of healthcare resource utilization will be summarized into a mean/median composite score, which may include the following: number and type (eg, respiratory, reactive airway disease [RAD]/asthma/wheezing) of medical visits (eg, outpatient, urgent care, emergency room, hospitalization, ICU), length of hospital stay, requirement for mechanical ventilation (yes/no, total number of episodes, total number of hours/days on treatment), requirement for IV fluids, requirement for respiratory diagnostic procedures (eg, chest radiograph, supplemental oxygen, pulse oximetry), 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 use days).

9.5. Interim Analyses

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 have occurred. Because of the relatively low number of cases of severe MA-LRTI due to RSV expected, the interim analysis will not consider that endpoint. Interim analysis results may be used for internal business decisions regarding future study planning, stopping for futility, stopping for early success, conducting a sample size reestimation, or adapting the study after the interim analysis.

The order of cases included in the interim analysis will be determined by the adjudication committee as those first confirmed as meeting the protocol-defined criteria. When the target number of cases for the interim analysis is reached, it is possible that additional potential cases will be under adjudication. These additional cases will be included in the interim analysis only if confirmed as cases by the EAC on the same day that the last per-protocol case is confirmed.

The analysis of efficacy will utilize an O'Brien-Fleming alpha spending rule based on the fraction of cases of MA-LRTI due to RSV available. For example, to control the overall type 1 error for the primary endpoint at 2.5% 1-sided, an interim analysis at 50% of the target number of cases would use a nominal 1-sided significance level of 0.14%. The final analysis

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at the target number of cases would use a nominal 1-sided significance level of 2.45%. The nominal alpha levels used at interim and final analyses will depend on the exact fraction of cases available at the interim analysis.

Testing of the primary endpoint at the interim analysis will follow the sequence of interval-specific tests as described in Section 9.4.1. However, consideration will be given to stopping the study for efficacy only if all time intervals through 180 days indicate statistically significant efficacy. Secondary endpoints will not be tested at the interim analysis.

Futility will also be assessed using conditional power. Full details will be defined in the SAP. For example, if there are 62 cases available for the interim analysis, Table 8 indicates case splits for which stopping the study will be considered. The actual number of cases available may be slightly higher or lower than 62, and the decision rules amended accordingly.

Table 8. 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
62	29	33	12% (-49%, 49%)	Conditional power <20%[b]; possible futility declaration
62	15	47	68% (24%, 88%)	Maximum number of RSV cases permitted to declare VE >20%

Abbreviation: VE = vaccine efficacy.
a. 99.7% confidence level for efficacy declaration; 95% confidence level for futility.
b. Other conditional power levels may be considered as a trigger for a futility decision.

Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's standard operating procedures (SOPs) will be documented and approved in the DMC charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

9.5.1. Data Monitoring Committee

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

The E-DMC will review safety data at defined intervals as specified in the charter. The E-DMC may conduct additional meetings to review safety data at other time points during the study, at its discretion, or at the request of the sponsor.

The E-DMC may review unblinded data during closed meeting sessions; however, the sponsor will remain blinded and will not be permitted access to the randomization assignments until the database is locked and unblinded.

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After each meeting, the E-DMC will make recommendations that may include continuing the study with or without modification or pausing or stopping vaccination for safety or other reasons.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

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of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the maternal participant and answer all questions regarding the study.

Maternal participants must be informed that their participation is voluntary. Maternal participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

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

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

Participants who are rescreened may be required to sign a new ICD as per IRB, local regulations, etc.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a

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product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents Within Marketing Authorization Packages/Submissions

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

Data Sharing

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

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

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10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the site Source Data Agreement Plan.

10.1.8. Study and Site Closure

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

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

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

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

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

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10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

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

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

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number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

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

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

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

10.2.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.2.2. Newly Diagnosed Chronic Medical Conditions (NDCMCs)

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 (eg, asthma).

10.2.3. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to

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whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

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Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study via occupational exposure	**None**	Occupational exposure (regardless of whether associated with an AE)

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

Assessment of Intensity

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

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

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3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

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

Assessment of Causality

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

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relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any anonymized postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

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- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

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10.4. Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.4) for the list of sponsor medical devices.

Medical Device Incident Definition

a. A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.

b. Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

a. A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.

b. A participant's study intervention is interrupted or compromised by a medical device

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failure.

c. A misdiagnosis due to medical device failure leads to inappropriate treatment.

d. A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation

a. Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF.

b. For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 2.

c. The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee.

d. It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

e. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

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10.5. Appendix 5: Background Factors

1. **Information on the following will be collected at Visit 1 for all infant participants:**

   - Educational level of parent(s) or legal guardian(s)
   - Exposure to smoke (including tobacco smoke)
   - Number of persons in the household
   - Number of children in the household and if they attend school
   - Number of children in the household under 5 years of age (under 60 months)
   - Number of children in the household ≥5 years of age (≥60 months)

2. **Information on the following will be collected at each postbirth visit, and at each MA-RTI visit:**

   - Childcare framework (for infant participants)
   - Breastfeeding information (including whether or not breastfeeding is exclusive)
   - Number of missed days of work for parent(s) or legal guardian(s) due to the infant participant's illness

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10.6. Appendix 6: Healthcare Provider Assessment and Treatment Criteria Checklist for MA-RTI Visit – Infant Participants

When an infant RTI medical visit criterion is met or confirmed, the site will obtain records from the medical visit and capture the healthcare information as detailed below in the eCRF. This information is based on respiratory-related assessments including examination findings, clinical findings, and any pathogen-related assessments/findings.

Medical Visit - visit details and assessment requirements

Note: This should not be linked to a study visit but may overlap with the MA-RTI assessment visit. The following fields and clinical assessment details should be obtained from relevant records for the medically attended event prior to each study-related MA-RTI assessment visit to support the assessment of the RTI event.

- **Reason for visit including date/time, eg,**
    - Nasal discharge for 24 hours or more.
    - Difficulty breathing, labored breathing, or rapid breathing for any duration.
    - Cough.
    - Inability to feed for any duration due to respiratory symptoms.
    - Any other respiratory symptom of concern (eg, apnea).
- Location of medical visit (inpatient clinic, outpatient clinic, emergency department, urgent care, hospitalization, home visit, other). ***Note: study visits should NOT be recorded here.***
    - **If hospital visit,** was this triggered by RTI or an SAE? (include details if associated with prolongation of hospitalization at birth). Provision of admission and discharge information and records, including ICU details.
- Clinical findings pertaining to respiratory symptoms and/or RTI, as detailed below but not limited to:
    - Presence or absence of respiratory examination findings, eg, chest wall indrawing, intercostal retractions, apnea (documented as per chart), failure to respond/unconsciousness.
    - Respiratory rate from highest/worst value of visit.
    - Oxygen saturation (SpO_2) from lowest/worst value of visit.
    - Altitude (select >1800 m OR ≤1800 m).

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- Oxygen supplementation (assisted ventilation, including type of respiratory assistance [respirator, “state-of-the-art” occlusive nasal prongs, face tent, etc]).
  - Days of supplementary oxygen.
  - Use of nasal cannula.
  - Use of high-flow nasal cannula or mechanical ventilation (ie, invasive or noninvasive).
- Heart rate from worst value of visit when performed consistently.
- Additional clinical or respiratory related assessments including chest x-ray

- Local test results for RSV as part of routine clinical care:
  - Testing platform used (clinical list of all platforms and validated by research).
  - Result (list: positive, negative, indeterminate, other).
- Obtain details of all prescribed medications including IV fluid usage.
- Obtain details of all AEs/SAEs in line with study requirements. Note: MA-RTIs are not AEs/SAEs.

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10.7. Appendix 7: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
AST	aspartate aminotransferase
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
dLIA	direct-binding Luminex immunoassay
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EAC	endpoint adjudication committee
EACC	endpoint adjudication committee charter
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDD	estimated delivery date
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine
GA	gestational age
GBS	group B streptococcal
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

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Abbreviation	Term
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
IUI	intrauterine insemination
IV	intravenous
IWR	interactive Web-based response
LFT	liver function test
LMIC	lower- and middle-income country
LMP	last menstrual period
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
N/A	not applicable
NAAT	nucleic acid amplification technology
NDCMC	newly diagnosed chronic medical condition
PCD	primary completion date
PCR	polymerase chain reaction
PFS	prefilled syringe
PT	prothrombin time
RAD	reactive airway disease
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus

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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
SMS	short message service
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
Tdap	tetanus, diphtheria, and acellular pertussis vaccine
ULN	upper limit of normal
US	United States
VE	vaccine efficacy

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090177e1926b8a9a\Approved\Approved On: 10-Dec-2019 16:28 (GMT)

Document Approval Record

Document Name:	C3671008 Clinical Protocol 05Dec2019
Document Title:	A PHASE 3, RANDOMIZED, DOUBLE- OR OBSERVER-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
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[redacted]	[redacted]	[redacted]

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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

Investigational Product Number:	PF-06928316
Investigational Product Name:	Respiratory Syncytial Virus (RSV) Vaccine
United States (US) Investigational New Drug (IND) Number:	017931
European Clinical Trials Database (EudraCT) Number:	2019-002943-85
ClinicalTrials.gov Identification (ID):	NCT04424316
Protocol Number:	C3671008
Phase:	3

Short Title: A Phase 3 Trial to Evaluate the Efficacy and Safety of RSVpreF in Infants Born to Women Vaccinated During Pregnancy.

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Document History

Document	Version Date
Protocol amendment 7	08 August 2022
Protocol amendment 6	01 June 2022
Protocol amendment 5	12 January 2022
Protocol amendment 4	22 March 2021
Protocol amendment 3	26 August 2020
Protocol amendment 2	26 June 2020
Protocol amendment 1	24 March 2020
Original protocol	05 December 2019

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs) and any global protocol administrative change letter(s) (PACL[s]).

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Protocol Amendment Summary of Changes Table

Amendment: 7 (08 August 2022)

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 2.2: Background	Reinstated the statistical analysis plan (SAP) from protocol amendment 5 and revised the alpha analysis for the study.	This change was made to address the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research's (CBER's) comments pertaining to protocol amendment 6	Substantial
Section 4.1: Overall Design	Reinstated the SAP from protocol amendment 5 and revised the alpha analysis for the study.	This change was made to address CBER's comments pertaining to protocol amendment 6	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.1.2: Approximate Number of Participants	Reinstated the SAP from protocol amendment 5 and revised the alpha analysis for the study.	This change was made to address CBER's comments pertaining to protocol amendment 6	Substantial
Section 9.2: Sample Size Determination	Reinstated the SAP from protocol amendment 5 and revised the alpha analysis for the study.	This change was made to address CBER's comments pertaining to protocol amendment 6	Substantial
Section 9.4.1: Efficacy Analysis	Reinstated the SAP from protocol amendment 5 and revised the alpha analysis for the study.	This change was made to address CBER's comments pertaining to protocol amendment 6	Substantial
Section 9.5: Interim Analyses	Reinstated the SAP from protocol amendment 5 and revised the alpha analysis for the study.	This change was made to address CBER's comments pertaining to protocol amendment 6	Substantial
Section 8.11.1: Infant Participants: Visit 1 – Birth (Hospital, Birth to 7 Days After Birth)	Added clarification regarding the collection of infant participant data, specifically the full date of birth on the study.	This is to provide clarification and ensure consistency with the study protocol requirements at investigational sites.	Nonsubstantial
Section 9.4.3.1: Immunogenicity Analysis	Deleted text pertaining to the maternal IgG subclass level immunogenicity analysis.	This is to align with the exploratory immunogenicity analysis planned for the study.	Nonsubstantial

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Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12 Appendix 12: Country-Specific Appendix – Applicable to New Zealand Only	Added a country-specific appendix for New Zealand that addresses the collection and overseas transfer of identifiable participant data, specifically the date of birth, to the Sponsor based on national regulatory laws and recommendations.	This change was made at the request of the New Zealand Health and Disabilities Ethics Committee (HDEC) to reflect local regulatory requirements as per PACL #12.	Nonsubstantial
Document History, Protocol Amendment Summary of Changes Table, and Section 10.13: Protocol Document History	Incorporated Pfizer protocol template text revisions to the document history and the summary of changes table. The previous amendment history has been moved to Section 10.13.	Not applicable (N/A)	Nonsubstantial
Protocol Title Page	Incorporated Pfizer protocol template revision to the protocol title page and added the study's Clinicaltrials.gov ID.	N/A	Nonsubstantial
Throughout	Minor editorial revisions as appropriate.	N/A	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Indication

Pfizer's respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF) is a prophylactic vaccine that is being investigated for the prevention of medically attended RSV-associated lower respiratory tract illness (LRTI) in infants by active immunization of pregnant women.

Rationale

There is a large unmet medical need that could be addressed by an effective RSV prophylaxis in infancy. Given the global burden of disease, maternal immunization offers an attractive strategy for infant disease prevention. Both preclinical studies in animals and interim data from a Phase 1/2 study in healthy nonpregnant adults have demonstrated acceptable tolerability and safety of RSVpreF. A robust immune response has also been observed in participants from the aforementioned trial. RSVpreF is currently under assessment in healthy pregnant women 18 through 49 years of age (Study C3671003: *A Phase 2b, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants; ClinicalTrials.gov identifier: NCT04032093*).

The safety and tolerability of RSVpreF in pregnant adolescents has yet to be demonstrated. Vaccine-elicited immune responses with RSVpreF are expected to be similar in adolescents and women based on studies comparing maternal immunization with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) and human papillomavirus (HPV) vaccines. Infants born to adolescent mothers are known to be at a higher risk of prematurity, an important risk factor for RSV disease. Therefore, pregnant adolescents (<18 years of age) are an appropriate pediatric population for RSVpreF maternal immunization, providing insight toward the efficacy, safety, and tolerability of the vaccine.

This randomized, double-blinded, placebo-controlled Phase 3 study is designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended lower respiratory tract illness (MA-LRTI) in infants.

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Objectives, Estimands, and Endpoints

Infant Participants

Primary Efficacy Objectives – Infant Participants	Estimands	Primary Efficacy Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	Vaccine efficacy (VE), defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI as confirmed by the endpoint adjudication committee (EAC): • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

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Primary Safety Objective – Infant Participants	Estimand	Primary Safety Endpoints – Infant Participants
To describe the safety of RSVpreF.	• In infant participants born to maternal participants receiving 1 dose of investigational product, the percentage of participants with each safety endpoint in each vaccine group.	• Specific birth outcomes. • Adverse events (AEs) from birth to 1 month of age. • Serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs): o from birth through 6 months of age (*first RSV season for all infant participants*). o from birth through 12 months of age (*for all infant participants*). o from birth through 24 months of age (*for infant participants born to maternal participants enrolled during the first year of the study*).
Secondary Efficacy Objectives – Infant Participants	**Estimands**	**Secondary Efficacy Endpoints – Infant Participants**
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Hospitalization due to RSV: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria. • occurring within 360 days after birth, if the analysis at 180 days meets efficacy criteria.

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To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	MA-LRTI due to any cause with protocol-defined criteria: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria. • occurring within 360 days after birth, if the analysis at 180 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	Vaccine efficacy (VE), defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI: • occurring within 210 days after birth. • occurring within 240 days after birth, if the analysis at 210 days meets efficacy criteria. • occurring within 270 days after birth, if the analysis at 210 days meets efficacy criteria. • occurring within 360 days after birth, if the analysis at 270 days meets efficacy criteria.

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Exploratory Objectives – Infant Participants	Estimands	Exploratory Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of medically attended respiratory tract illness (MA-RTI) due to RSV.		RSV-positive MA-RTI: • occurring within 90 days after birth. • occurring within 120 days after birth. • occurring within 150 days after birth. • occurring within 180 days after birth. • occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI.		The incidence of all-cause MA-RTIs from vaccination up to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV in infants after 12 months of age.		MA-LRTIs due to RSV occurring 361 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV in infants after 6 months of age.		Severe MA-LRTIs due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV in infants after 6 months of age.		Hospitalization due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI in infants after 6 months of age.		MA-LRTIs due to any cause occurring 181 to 730 days after birth.
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.		RSV subgroup A– and subgroup B–specific MA-LRTI.
To describe the non-RSV infectious etiology of MA-RTI in the study population.		Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits.
To evaluate RSV serum neutralizing titers elicited by RSVpreF and transferred transplacentally.		RSV A and RSV B serum neutralizing titers measured at birth.
To assess the impact of RSVpreF on RSV illness based on socioeconomic factors.		Primary and secondary efficacy by select demographic risk factors (eg, breastfeeding, maternal smoking, number of household members).

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To assess the effect of RSVpreF on healthcare utilization.		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 intravenous (IV) fluids, requirement for prescriptions, and antibiotic use.
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.		MA-RTI, MA-LRTI, and severe MA-LRTI due to RSV occurring 0 to 730 days after birth.

Maternal Participants

Primary Safety Objective – Maternal Participants	Estimand	Primary Safety Endpoints – Maternal Participants
To describe the safety and tolerability of RSVpreF.	In maternal participants receiving 1 dose of investigational product, the percentage of maternal participants with each safety endpoint in each vaccine group.	The incidence of: • 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 (*Visit 1 through the 6-month-postdelivery study visit*).
Exploratory Objectives – Maternal Participants	**Estimands**	**Exploratory Endpoints – Maternal Participants**
To describe MA-RTI in this study population.		The incidence of all-cause MA-RTIs from vaccination up to 180 days after delivery.
To evaluate the immune responses elicited by RSVpreF.		• RSV A and RSV B serum neutralizing titers and prefusion F immunoglobulin G (IgG) titers measured: • before vaccination. • at delivery.

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Overall 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, as well as 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 the statistical analysis section [Section 9.2]). There is no specific case target for the additional primary endpoint of severe MA-LRTI. The total enrollment number of maternal participants may vary depending on the incidence rate of the primary endpoint in the infant participants, the true underlying VE, and a potential early stop for efficacy or futility. In the event that efficacy in the infant population is demonstrated at an interim analysis, enrollment of maternal participants may continue in order to obtain safety evaluations in an adequate number of maternal and infant participants to support vaccine registration with national health authorities.

Based on these considerations, and in order to accumulate endpoint cases, 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 coronavirus disease 2019 (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 cases of RSV.

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

Once they have provided informed consent, the women will be referred to as "maternal participants" and will be followed from vaccination during pregnancy until 6 months after delivery. Assessments will include parameters to allow descriptions of safety, tolerability, and immunogenicity of the vaccine in maternal participants. **Note:** *Maternal participants will include adolescent females who may be referred to as "minors." Information/assessments for minors may require parental/legal guardian awareness/approval per local regulations.*

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Infants born to women who receive RSVpreF or placebo in their second or third trimester will be referred to as "infant participants." Infant participants born to women enrolled during the first year of the study will have 6 scheduled study visits during their 24 months of participation, whereas all other infant participants will have up to 4 scheduled study visits during their 12 months of participation. 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. For infant participants enrolled during the first year of the study, the extended 12-month study duration will involve longer-term respiratory tract illness (RTI) surveillance and safety oversight to address safety and the possibility of conferred enhanced protection (antibody persistence) during a second RSV season.

All MA-RTIs meeting the protocol definition for a potential study endpoint will be adjudicated by an independent adjudication committee.

Planned Duration

Pregnant women will participate in the study from enrollment during their pregnancy, and for approximately 6 months after delivery of their infants. The total duration will be up to approximately 10 months, depending on gestational age (GA) at the time of vaccination and when the infant is actually born.

All eligible infant participants born to enrolled maternal participants during the first year of the study will participate in the study from the time of birth and will be followed for up to 24 months for RSV surveillance and safety for the secondary and exploratory endpoints of the study. All other infants will participate from the time of birth and for at least 12 months after birth.

Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC) to monitor vaccine safety and efficacy and study futility.

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Statistical Methods

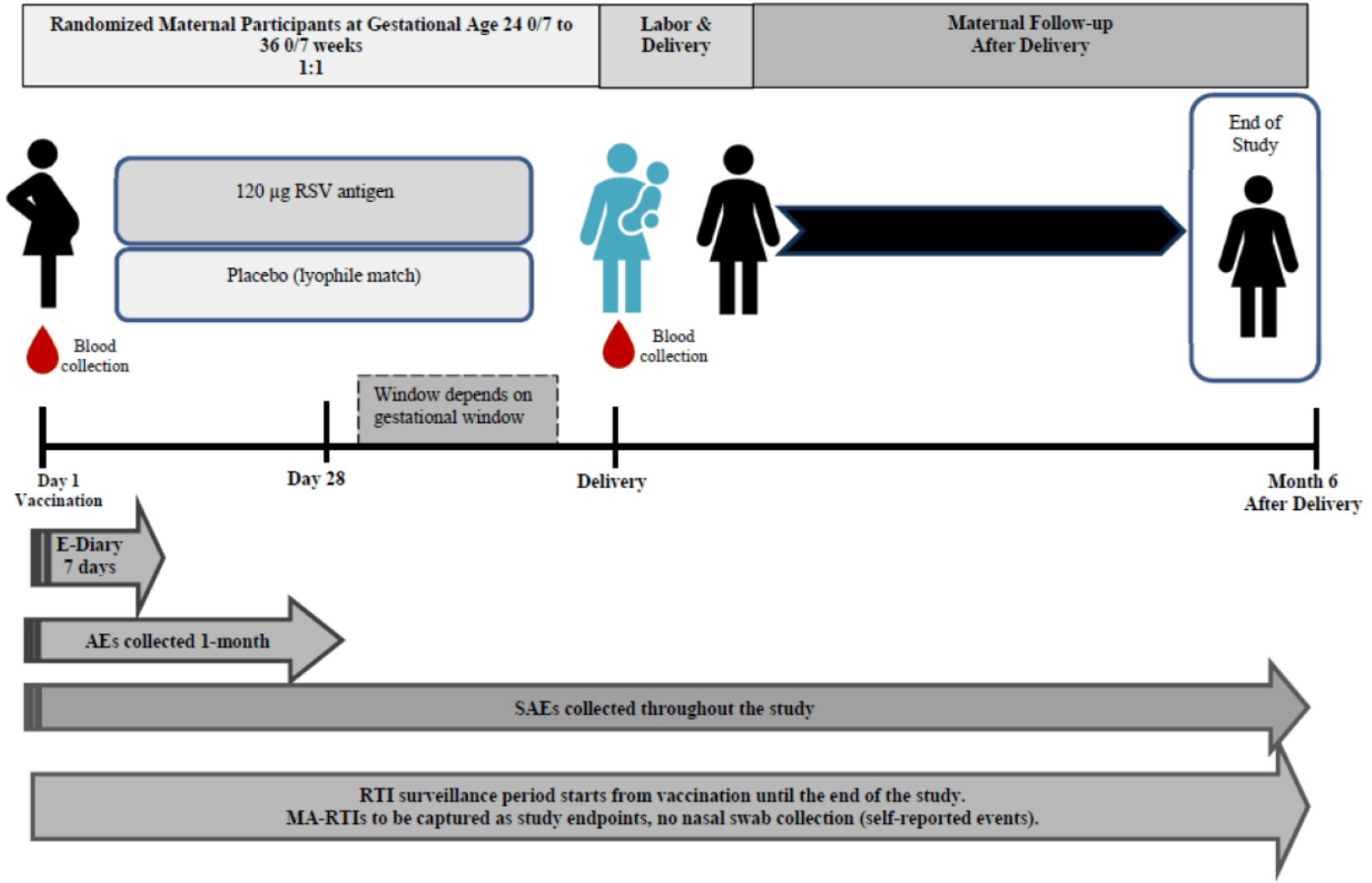
The primary hypothesis to be tested is that VE with respect to MA-LRTI due to RSV or severe MA-LRTI due to RSV in infants within at least 90 days after birth is more than 20%, relative to placebo. The 2 primary endpoints will be tested in parallel using a multiplicity adjustment procedure. VE will be estimated using the exact conditional binomial method. There will also be hierarchical testing of the primary endpoints to 120 days, 150 days, and 180 days, conditional on success of the analysis for the shorter intervals. Interim analyses of the MA-LRTI-due-to-RSV endpoint with the opportunity to stop the study for efficacy or futility may be included. At the end of the trial, the RSV vaccine may be deemed efficacious if there are 42 or fewer cases of MA-LRTI due to RSV in the RSV vaccine group out of the 124 total primary-endpoint cases at 90 days. This corresponds to an estimated VE = 49%, with a 97.6% confidence interval (CI) = (21%, 68%). For severe MA-LRTI, assuming a total of 50 cases occur, the vaccine may be deemed efficacious if there are 13 or fewer cases in the RSV vaccine group. This corresponds to an estimated VE = 65%, with a 97.6% CI = (26%, 85%).

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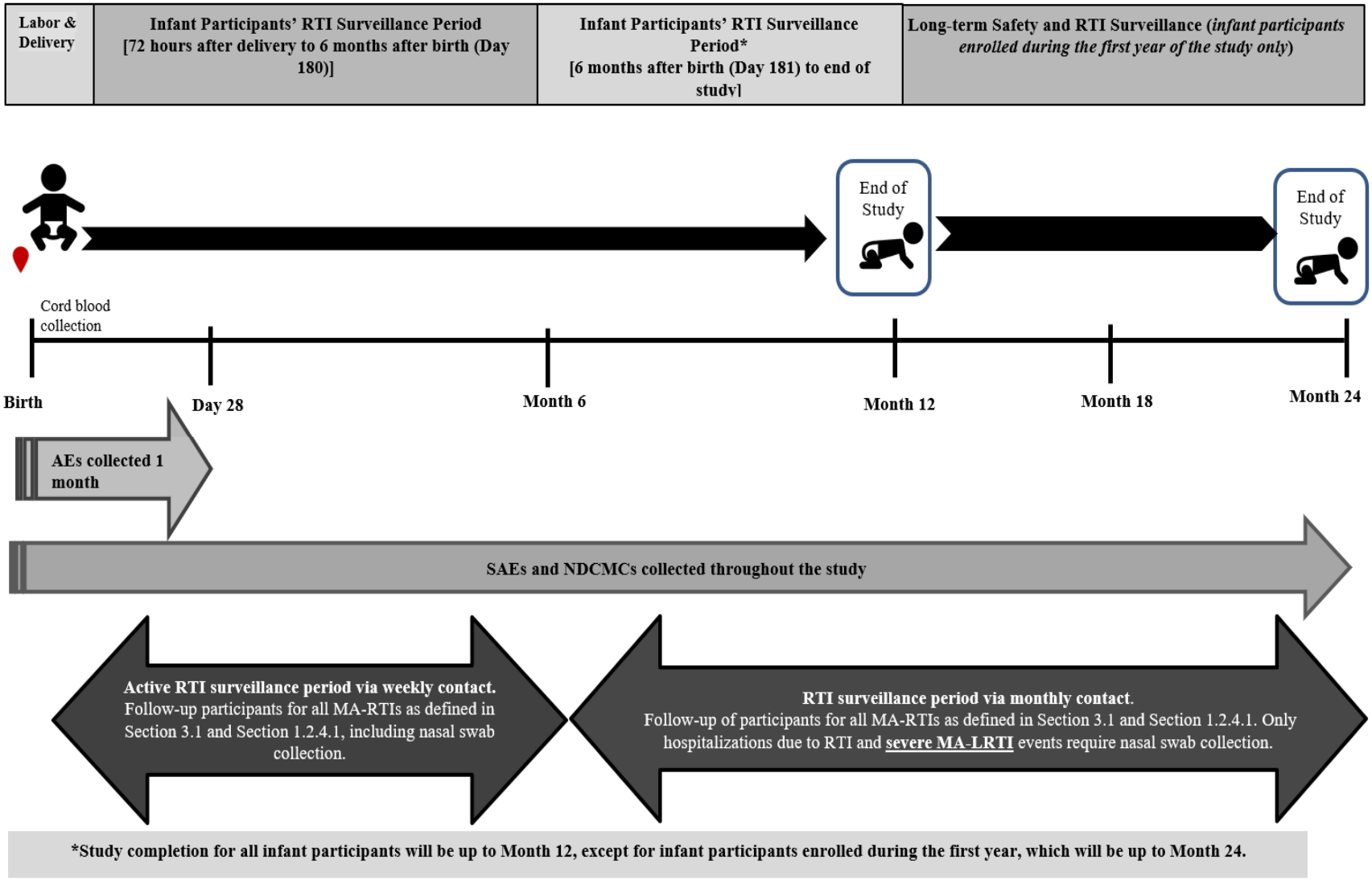
1.2. Schematic for Study Participants

1.2.1. Study Design – Maternal Participants



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1.2.2. Study Design – Infant Participants



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Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.2.3. Schedule of Activities for Maternal Participants

Visit Description	Screening and Vaccination[a]	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	**28 Days Prior to Vaccination to Day 1**	**28 to 42 Days After Vaccination**		**180 to 210 Days After Delivery**
Type of Visit	**Clinic**	**Clinic or Telephone**	**Maternity Unit**	**Clinic, Home, or Telephone**
Informed consent for maternal participant and her infant	X			
Assign single maternal participant identifier	X			
Demography	X			
Medical history including obstetric history[d]	X			
Record current/former alcohol, tobacco, marijuana, or any illicit drug usage	X			
Record vital signs	X			
Targeted physical and obstetric examination performed on the same day or within 7 days before the vaccination visit	X			
Record details of any antenatal and/or postnatal steroid treatment, monoclonal antibodies, blood products, or Rho(D) immune globulin	X	X	X	X
Record details of the maternal participant's GBS status and if any medication was given for IAP			X	
Record nonstudy vaccine information	X	X	X	X
Review eligibility criteria	X	X	X	
Review temporary delay criteria	X			

Visit Description	Screening and Vaccination[a]	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	**28 Days Prior to Vaccination to Day 1**	**28 to 42 Days After Vaccination**		**180 to 210 Days After Delivery**
Type of Visit	**Clinic**	**Clinic or Telephone**	**Maternity Unit**	**Clinic, Home, or Telephone**
Prevaccination blood draw for serologic assessment (~15 mL) on the same day or within 7 days before the vaccination visit	X[e]			
Assign randomization and container number	X			
E-diary training, dispense digital thermometer and measuring device[f]	X			
Obtain and record baseline assessment of prespecified systemic events **on the day of and prior to vaccination** in the e-diary	X			
Administer investigational product	X			
Postvaccination observation (at least 30 minutes) and assessment of immediate AEs	X			
Delivery blood draw for serologic assessment (~15 mL)			X[e]	
Record pregnancy outcome information			X	
Review e-diary data[g]	X----------X			
Record AEs, as appropriate[h]	X----------X			
Record SAEs, as appropriate[h]	X	X	X	X

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Visit Description	Screening and Vaccination[a]	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	28 Days Prior to Vaccination to Day 1	28 to 42 Days After Vaccination		180 to 210 Days After Delivery
Type of Visit	Clinic	Clinic or Telephone	Maternity Unit	Clinic, Home, or Telephone
Record details pertaining to MA-RTI visit[i]	Assessment of confirmed MA-RTI events during the study as detailed in Section 1.2.3.1 of the schedule of activities			

Abbreviations: CRF = case report form; e-diary = electronic diary; GBS = group B streptococcal; IAP = intrapartum antibiotic prophylaxis; ICD = informed consent document; MA-RTI = medically attended respiratory tract illness.

a. In countries/locales where certain prenatal assessments are not routinely performed, prerandomization assessments and test results to confirm maternal participant eligibility for this clinical trial can be obtained and reviewed by the investigator or qualified designee up to 28 days prior to vaccination.
b. The 1-month follow-up visit will not be performed if delivery occurs before this visit. Active elicitation and collection of AEs and SAEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination. Once delivery occurs, the visit windows are calculated based on the delivery date.
c. The delivery visit includes the time from when a participant is admitted into labor through discharge following delivery of her infant. Please see Section 8.10.3 for required protocol assessments at this visit.
d. Where an obstetric ultrasound examination is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination. As part of the obstetric history, details regarding the LMP and estimated delivery date (EDD) are to be recorded.
e. AEs occurring up to 48 hours after a blood draw that are related to the study procedures must be reported in the CRF.
f. Maternal participants will be issued a measuring device to measure local reactions and a digital thermometer for recording daily temperatures and will be provided with instructions on their use. Maternal participants and/or the study staff/field worker (as per local practice) will record (in an e-diary) a baseline assessment of prespecified systemic events on the day of and prior to vaccination and reactogenicity events from Day 1 to Day 7 following vaccination (where Day 1 is the day of vaccination). Remind maternal participants and their parent(s)/legal guardian (if a minor) that the study staff/field worker may contact them to obtain additional information on events entered into the e-diary. Ask maternal participants or their parent(s)/legal guardian (if a minor) to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination, to determine if an unscheduled reactogenicity visit is required. Based on local rules of practice, the maternal participant may be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns.
g. Site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate maternal participant compliance and as part of the ongoing safety review.
h. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs through 28 days after vaccination. From the signing of the ICD until the maternal participant completes the study, all SAEs will be collected. Please see Section 8.3.1 for reporting requirements and timelines.
i. A confirmed MA-RTI is defined as an expected RTI event based on the assessments detailed in the schedule of assessments in Section 1.2.3.1. These events will not be captured as safety events, unless the investigator or an appropriate designee deems them to be related to the investigational product or to have resulted in death.

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1.2.3.1. Schedule of Activities for Maternal Participants: RTI Surveillance for Medically Attended Respiratory Tract Illness Visits (Vaccination Until the End-of-Study Visit)

Visit Description	Assessments of MA-RTI[a]
Visit Window	**As Soon as Possible After Confirmed MA-RTI**
Type of Visit	**Telephone**
Record details of a confirmed MA-RTI	X
Details of an acute illness visit AND a report of 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	X
Obtain standard-of-care records, including local NAAT testing results (if applicable)[b]	X
Record nonstudy vaccine information	X
Record AEs and SAEs, as appropriate[c]	X
Complete the CRF with details	X

Abbreviations: CRF = case report form; MA-RTI = medically attended respiratory tract illness; NAAT = nucleic acid amplification technology; RSV = respiratory syncytial virus; RTI = respiratory tract illness.

a. Confirmed cases of MA-RTI will be collected from vaccination until the maternal participant completes the study. The assessment of the event would involve a telephone call, or a clinic visit if determined by the investigator to be warranted.
b. Site staff will review and collect data pertaining to the illness and any local NAAT testing results (RSV, influenza, etc), if available.
c. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs and SAEs through 28 days after vaccination. From 28 days after vaccination until the maternal participant completes the study, all SAEs will be collected. MA-RTI events will not be captured as safety events, unless the investigator or an appropriate designee deems them to be related to the investigational product or to have resulted in death. Please see Section 8.3.1 for reporting requirements and timelines.

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1.2.4. Schedule of Activities for Infant Participants

Participants	All Infant Participants				Long-Term Follow-up for Infant Participants Enrolled in the First Year of the Study[a]	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Visit Description	**Birth**	**1-Month Follow-up[b]**	**6-Month Follow-up[b]**	**12-Month Follow-up**	**18-Month Follow-up**	**24-Month Follow-up**
Visit Window (Days)	**Birth to 7 Days After Birth**	**28 to 48 Days After Birth**	**180 to 210 Days After Birth**	**350 to 378 Days After Birth**	**525 to 574 Days After Birth**	**714 to 742 Days After Birth**
Type of Visit	**Hospital**	**Clinic or Home**	**Clinic or Home**	**Clinic or Telephone**	**Clinic or Telephone**	**Clinic or Telephone**
Assign infant participant identifier	X					
Demography	X					
Collect background factors[c]	X	X	X	X	X	X
Collect birth outcome information including infant's birth data and appearance, pulse, grimace, activity, and respiration (Apgar) score	X					
Obtain and record infant's length, head circumference, and weight	X	X	X	X (if clinic visit)		X (if clinic visit)
Physical examination including vital signs (temperature, heart rate, SpO_2 by pulse oximetry, and respiratory rate) performed within 72 hours after birth	X					
Obtain and record vital signs, including temperature, heart rate, SpO_2 by pulse oximetry, and respiratory rate		X				
Targeted physical examination (record in the site source document)		X	X	X (if clinic visit)		X (if clinic visit)
Record immune globulins, monoclonal antibodies (eg, Synagis), or blood products (eg, whole blood, packed cells)	X	X	X	X	X	X
Review eligibility	X					
Cord blood sample (~10 mL) for serologic assessment[d]	X					
Record AEs, as appropriate[e]	X					
Record NDCMCs and SAEs, as appropriate[e]	X	X	X	X	X	X

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Participants	All Infant Participants				Long-Term Follow-up for Infant Participants Enrolled in the First Year of the Study[a]	
Visit Number	1	2	3	4	5	6
Visit Description	Birth	1-Month Follow-up[b]	6-Month Follow-up[b]	12-Month Follow-up	18-Month Follow-up	24-Month Follow-up
Visit Window (Days)	Birth to 7 Days After Birth	28 to 48 Days After Birth	180 to 210 Days After Birth	350 to 378 Days After Birth	525 to 574 Days After Birth	714 to 742 Days After Birth
Type of Visit	Hospital	Clinic or Home	Clinic or Home	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone
Surveillance reminder contact	Contact with the infant participants' parent(s) or legal guardian(s) approximately every week until Visit 3		From Visit 3, contact with the infant participant's parent(s) or legal guardian(s), approximately every 28 to 35 days until the end of the study			
Assessment of MA-RTIs[f,g]	Assessment of MA-RTI events during the active RSV surveillance period as detailed in Section 1.2.4.1 of the schedule of activities		Assessment of MA-RTI events as detailed in Section 1.2.4.1 of the schedule of activities			

Abbreviations: MA-RTI = medically attended respiratory tract illness; NDCMC = newly diagnosed chronic medical condition; RSV = respiratory syncytial virus; SpO_2 = oxygen saturation.

a. Applicable only for infant participants enrolled during the first year of the study.
b. If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster), study visits that cannot be conducted in the clinic or at home, in accordance with the protocol requirements, may be conducted via telephone.
c. Background factors as detailed in Appendix 5 related to socioeconomic and health factors that may impact the incidence of RSV illness.
d. Cord blood must be obtained on the day of birth. Cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been clamped and cut. If cord blood is unavailable, a blood sample may be collected from the infant participant preferably within the first 24 hours but up to 7 days after birth. The infant's weight must be used to determine the volume of blood that can be collected.
e. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs, NDCMCs, and SAEs through 28 days after birth. From 29 days after birth until the infant participant completes the study, NDCMCs and SAEs will be collected. 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 (eg, asthma).
f. A confirmed MA-RTI is defined as an expected study event based on the assessments detailed in the schedule of assessment in Section 1.2.4.1. These events will not be captured as safety events, unless the investigator or an appropriate designee deems them to be related to the investigational product or to have resulted in death.
g. Reporting MA-RTI events should commence 72 hours after the infant's delivery. Respiratory distress events associated with and within 72 hours of birth should not be captured as MA-RTI events on the study but should be captured as AEs/SAEs (if applicable).

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1.2.4.1. Schedule of Activities for Infant Participants: Respiratory Tract Illness Study Visits During the Study

Assessment Period During the Study	Birth to 180 Days After Birth	181 Days After Birth to the End of the Study	
Visit Window (Days)	As Soon as Possible After Confirmed MA-RTI and Within 72 Hours (Preferable) or Up to 10 Days	As Soon as Possible After Confirmed MA-RTI and Within 72 Hours (Preferable) or Up to 10 Days	
Type of Visit	RTI Study Visit for All MA-RTI[a] Hospital, Home, or Clinic	Follow-Up for MA-RTI Visit Telephone	RTI Study Visit for Hospitalization or Severe MA-LRTI[b] Hospital, Home, or Clinic
Surveillance reminder contact	Contact the infant participants' parent(s) or legal guardian(s) approximately every week until Visit 3	From Visit 3, contact the infant participants' parent(s) or legal guardian(s), approximately every 28 -35 days until the end of the study	
Record confirmed MA-RTI as detailed in Appendix 6, as appropriate	X	X	X
Record details of the RTI, including 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	X	X	X
Obtain standard-of-care records and complete CRF[c]	X	X	X
Record local NAAT testing results, if performed and available[d]	X	X	X
Perform RTI study visit, record targeted assessment results (temperature, heart rate, respiratory rate, SpO_2 by pulse oximetry, chest wall indrawing) and body weight, and collect nasal swab (for RT-PCR)[e]	X		X
Record concomitant medication associated with the treatment of the MA-RTI	X	X	X

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Assessment Period During the Study	Birth to 180 Days After Birth	181 Days After Birth to the End of the Study	
Visit Window (Days)	As Soon as Possible After Confirmed MA-RTI and Within 72 Hours (Preferable) or Up to 10 Days	As Soon as Possible After Confirmed MA-RTI and Within 72 Hours (Preferable) or Up to 10 Days	
Type of Visit	RTI Study Visit for All MA-RTI[a] Hospital, Home, or Clinic	Follow-Up for MA-RTI Visit Telephone	RTI Study Visit for Hospitalization or Severe MA-LRTI[b] Hospital, Home, or Clinic
Collect background factors associated with MA-RTI[f]	X	X	X
Record immune globulins, monoclonal antibodies (eg, Synagis), or blood products (eg, whole blood, packed cells)	X	X	X
Record AEs , NDCMCs, and SAEs, as appropriate[g]	X	X	X
Compile MA-RTI visit source documentation upon request by adjudication committee (qualifying RSV-positive cases only)	X		X

Abbreviations: CRF = case report form; HCP = healthcare provider; ICU = intensive care unit; IV = intravenous; MA-LRTI = medically attended lower respiratory tract illness; MA-RTI = medically attended respiratory tract illness; NAAT = nucleic acid amplification technology; NDCMC = newly diagnosed chronic medical condition; RSV = respiratory syncytial virus; RTI = respiratory tract illness; RT-PCR = reverse transcription–polymerase chain reaction; SpO_2 = oxygen saturation.

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Assessment Period During the Study	Birth to 180 Days After Birth	181 Days After Birth to the End of the Study	
Visit Window (Days)	As Soon as Possible After Confirmed MA-RTI and Within 72 Hours (Preferable) or Up to 10 Days	As Soon as Possible After Confirmed MA-RTI and Within 72 Hours (Preferable) or Up to 10 Days	
Type of Visit	RTI Study Visit for All MA-RTI[a] Hospital, Home, or Clinic	Follow-Up for MA-RTI Visit Telephone	RTI Study Visit for Hospitalization or Severe MA-LRTI[b] Hospital, Home, or Clinic

a. If the infant participant is reported to be experiencing or has had an MA-RTI from birth until Visit 3, the site should arrange a study visit as soon as possible and within 72 hours (preferable) or up to 10 days. Ideally, the RTI study visit will be conducted at the investigational study site; however, it is possible that the visit could be conducted in another healthcare setting (for example, if the infant participant is hospitalized) or the site staff may visit where the infant participant is residing. Note: Reporting MA-RTI events should commence 72 hours after the infant's delivery.

b. If the infant participant is reported to be experiencing or has had an MA-RTI associated with severe LRTI criteria or been hospitalized for an RTI from Visit 3 until the end of study participation, the site should arrange a RTI study (SRTI) visit as soon as possible and within 72 hours (preferable) or up to 10 days of the MA-RTI visit. Ideally, assessment of these potential endpoint events (hospitalization due to RTI or severe MA-LRTI) will be conducted at the investigational study site; however, it is possible that the visit could be conducted in another healthcare setting (for example, if the infant participant is hospitalized) or the site staff may visit where the infant participant is residing. Note: For nonsevere MA-RTIs, a telephone contact with the infant participants' parent(s) or legal guardian(s) is acceptable to complete the follow-up assessments.

c. Obtain case records, including details of hospitalization, ICU stays, use of oxygen, IV fluids usage, etc.

d. The site staff/field worker will review and collect data related to any local NAAT testing results, if performed and available.

e. The site staff/field worker will collect nasal swabs for confirmed MA- RTIs, including confirmed cases of hospitalizations due to an RTI and severe MA-LRTIs. In the event that restrictions prevent taking RTI study swabs because of an outbreak, pandemic situation, or natural disaster, the study nasal swab can be collected for processing at Pfizer's central laboratory by the infant caregiver, during or within 10 days following an MA-RTI visit, or by the HCP assessing the infant during the MA-RTI visit (in addition to any samples obtained in the course of routine clinical care) as detailed in Section 8.11.7.1 and Section 8.11.8.

f. Background factors as detailed in Appendix 5 related to socioeconomic and health factors that may impact the incidence of RSV. This will be collected for all MA-RTI events reported.

g. The investigator and site staff/field worker will ensure the active elicitation and collection of NDCMCs and SAEs through the end-of-study visit for the infant participant. From 29 days after birth until the infant participant completes the study, NDCMCs and SAEs will be collected. 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 (eg, asthma). Note: A confirmed MA-RTI will not be captured as a safety event, unless the investigator or an appropriate designee deems it to be related to the investigational product or to have resulted in death.

2. INTRODUCTION

Prevention of RSV disease in young infants is a significant unmet medical need globally. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in those with risk factors including premature infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems.[1] However, most cases of RSV disease occur in healthy, full-term infants without risk factors.[2] Worldwide, RSV kills approximately 118,200 children annually, with about half of those deaths occurring in infants under 6 months of age, and the majority of those occurring in resource-limited countries.[3,4] In the United States (US), RSV is the leading cause of infant hospitalization, with more than 60,000 hospitalizations of children 12 months of age and younger annually.[5,6] There is increasing evidence that the link between severe RSV disease in infancy and wheezing later in childhood may be causal.[7,8] Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall.[9] Infection is essentially universal by the time children reach 2 years of age.[10]

Currently, there is neither specific treatment for RSV infection nor a vaccine to protect against RSV disease. Treatment consists primarily of supportive care. A prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), targeting the RSV F glycoprotein is available for prevention of severe RSV disease in young infants at increased risk.[11] Limitations of its use include its high cost[12] and requirement of multiple monthly injections,[13] and so it remains recommended for use only in very premature infants and others at increased risk of severe illness.[6,14]

Nevertheless, the protective effect of Synagis provides definitive proof of principle that serum neutralizing antibody directed against the F protein can provide clinically meaningful protection against RSV lower respiratory tract disease in young infants.[15] Furthermore, it is well known that in other disease settings, antibodies transferred from mothers to their fetuses across the placenta can reduce infant disease early in life,[16,17,18,19,20,21] suggesting that maternal immunization is a reasonable approach to RSV disease prevention among young infants.

There are 2 antigenic variants of RSV, namely, RSV subgroup A (RSV A) and RSV subgroup B (RSV B). The RSV vaccine being investigated in this study is a bivalent vaccine composed of stable RSV prefusion F antigens representing the 2 subgroups to help ensure the broadest coverage against RSV illness.

RSVpreF is a prophylactic vaccine being developed to prevent medically attended RSV-associated LRTI in infants by active immunization of pregnant women.

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2.1. Study Rationale

There is a large unmet medical need that could be addressed by an effective RSV prophylaxis in infancy. Given a global burden of disease in the millions of cases each year, maternal immunization offers an attractive strategy for infant disease prevention. Both preclinical studies in animals and interim data from a Phase 1/2 study in healthy nonpregnant adults have demonstrated acceptable tolerability and safety of RSVpreF. A robust immune response has also been observed in the population of the aforementioned trial, at 1 month after vaccination. The combined RSV A and B serum neutralization geometric mean titers (GMTs) have been shown to be 12 to 20 times higher than those with 100 µg/mL of palivizumab, the concentration of the monoclonal antibody that is known to provide near to complete protection of high-risk infants from severe RSV disease.[22,23] RSVpreF is currently under assessment in healthy pregnant women 18 through 49 years of age (Study C3671003, *A Phase 2b, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants; ClinicalTrials.gov identifier: NCT04032093)*.

The safety and tolerability of RSVpreF in pregnant adolescents has yet to be demonstrated. Vaccine-elicited immune responses with RSVpreF are expected to be similar in adolescents and women based on studies comparing maternal immunization with Tdap and HPV vaccination.[24,25,26] Infants born to adolescent mothers are known to be at a higher risk of prematurity, an important risk factor for RSV disease.[27,28] Therefore, pregnant adolescents (<18 years of age) are an appropriate pediatric population for RSVpreF maternal immunization, providing insight toward the efficacy, safety, and tolerability of the vaccine.

This randomized, double-blinded, placebo-controlled Phase 3 study is designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended RSV-associated LRTI in infants.

2.2. Background

RSV is an important cause of morbidity and mortality worldwide, with a substantial burden of disease borne by young infants. Rates of severe RSV illness are highest in infants <6 months of age, with a peak in hospitalization between 1 and 2 months of life, though the highest case-fatality rates are observed in the neonatal period (<1 month).[2] Infants born prematurely and those with underlying cardiac or pulmonary disease are at further increased risk of severe clinical disease due to RSV. A 2017 retrospective case analysis that examined RSV mortality data from 23 countries demonstrates the global nature of the seriousness of RSV disease, with significant morbidity and mortality occurring in both lower- and middle-income countries (LMICs) and high-income countries.[3,4]

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No specific treatments for RSV exist, and available prophylactic measures (ie, RSV monoclonal antibody) are limited to use in only those infants at highest risk; additionally, in LMICs, use of available RSV prophylaxis is cost-prohibitive. While active immunization against RSV in infants might be an option, multiple efforts, extending over half a century, to develop a safe and effective RSV vaccine to protect infants from disease have yielded little success. The early peak of disease presents a further obstacle to an active vaccination strategy for infants. Given these challenges, maternal immunization to protect infants early in life offers an attractive strategy for infant disease prevention.

The present RSV vaccine efforts were initiated in early 2014 based on a new scientific discovery (determination of the RSV prefusion F crystal structure)[29] and a changing regulatory and policy environment that today supports the development of vaccines for maternal immunization to protect very young infants. The trimeric RSV F surface glycoprotein in a prefusion conformation is now known to be the primary target of neutralizing antibodies and is the basis for the engineered antigens in Pfizer's vaccine candidate. Applying structure-guided vaccine design, Pfizer has developed a stabilized RSV prefusion F vaccine candidate. The core hypothesis underlying Pfizer's RSV vaccine development effort for prevention of infant disease is that vaccine antigens based on RSV prefusion F, when administered to pregnant women in the second or third trimester of pregnancy, will elicit sufficiently high neutralizing antibody titers that, when the antibodies are actively transferred transplacentally to the fetus, will protect infants against RSV disease. The aim is for neutralizing antibody levels to be at sufficient levels such that infants will be protected from birth and possibly through their first RSV season.

2.3. Benefit/Risk Assessment

RSVpreF is being evaluated in ongoing clinical studies. Pfizer's maternal immunization approach circumvents the risk of vaccine-mediated disease enhancement that was observed in the 1960s following direct immunization of RSV-naive infants with a formalin-inactivated RSV vaccine (FI-RSV).[30] FI-RSV elicited a predominantly nonneutralizing antibody response and a Th2-biased cell-mediated response, both of which are considered potential contributing factors to disease enhancement.[31] During preclinical studies, in a standard cotton rat infectious RSV challenge model, FI-RSV showed pathological signs of causing disease enhancement, and the current Pfizer vaccine candidate, RSVpreF, did not. Most important, RSV vaccine–mediated disease enhancement has not been reported to occur in RSV-experienced individuals after immunization with any RSV vaccine candidate. Because pregnant women are universally RSV-experienced, they are not considered at risk for a disease-enhancing immune response to the vaccine that could exacerbate infection in themselves. Enhanced disease has not been observed in infants born to mothers who received prior investigational RSV vaccines; therefore, enhanced disease in infants is very unlikely. A previous study of maternal immunization with a Wyeth (later merged with Pfizer) investigational RSV vaccine (PFP-2) showed an acceptable safety profile, even though this candidate contained a postfusion RSV F antigen that elicited a relatively weak RSV-neutralizing antibody response and a higher nonneutralizing RSV-binding antibody response in pregnant women.[32] A recently completed Phase 3 maternal RSV trial (Novavax) with an RSV vaccine containing F not stabilized in the prefusion form, given to over

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4600 healthy pregnant volunteers, showed a similar safety profile in the RSV vaccine and placebo groups.[33]

Vaccination with the RSV prefusion F antigens elicit a higher ratio of neutralizing to nonneutralizing antibodies, more closely matching the profile in naturally exposed individuals. The safety profile of RSVpreF observed to date is similar to that of prior RSV F subunit vaccines tested in RSV-experienced adults.

There are limited data on the global burden of maternal RSV infection, likely in part because of infrequent diagnostic testing. However, in one multisite study, RSV-associated disease in pregnancy was shown to result in prolonged hospitalization and an increased likelihood of preterm birth in women who tested RSV-positive.[34] It is possible that vaccination may benefit the pregnant women who receive it. RTI in mothers who receive RSVpreF will be explored in this study. The benefit of maternal vaccination is accrued to the infant by means of transplacental antibody transfer.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of RSVpreF may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

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3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. Infant Participants

The study objectives and endpoints for infant participants employ the event definitions in Table 1.

Table 1. Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
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 laboratory with NAAT for RSV
MA-RTI due to RSV[b]	• An MA-RTI visit **AND** • RSV-positive test result as described in Section 8.1.1.1
MA-LRTI due to any cause	• Infant with an MA-RTI visit **AND** • Fast breathing (RR ≥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
MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 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
Hospitalized RTI due to RSV[b]	An RTI due to RSV that results in hospitalization

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Table 1. Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
Severe MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥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 (ie, 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
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by an EAC

Abbreviations: bpm = breaths per minute; 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 technology; RR = respiratory rate; RSV = respiratory syncytial virus; RTI = respiratory tract illness; SpO_2 = oxygen saturation.

a. RSV-positive testing is defined as a positive RSV test (see Section 8.1.1.1) conducted on a sample obtained during the medically attended visit or within 10 days (where Day 1 is the day of the MA-RTI visit) as detailed in Section 8.11.7.

b. The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTI visit and RTI study visits, including all available RSV test results.

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Study Objectives – Infant Participants

Primary Efficacy Objectives – Infant Participants	Estimands	Primary Efficacy Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

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Primary Safety Objective – Infant Participants	Estimand	Primary Safety Endpoints – Infant Participants
To describe the safety of RSVpreF.	• In infant participants born to maternal participants receiving 1 dose of investigational product, the percentage of participants with each safety endpoint in each vaccine group.	• Specific birth outcomes. • AEs from birth to 1 month of age. • SAEs and NDCMCs: o from birth through 6 months of age *(first RSV season for all infant participants).* o from birth through 12 months of age *(for all infant participants).* o from birth through 24 months of age *(for infant participants born to maternal participants enrolled during the first year of the study).*
Secondary Efficacy Objectives – Infant Participants	**Estimands**	**Secondary Efficacy Endpoints – Infant Participants**
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Hospitalization due to RSV: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria. • occurring within 360 days after birth, if the analysis at 180 days meets efficacy criteria.

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To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	MA-LRTI due to any cause with protocol-defined criteria: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria. • occurring within 360 days after birth, if the analysis at 180 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	Vaccine efficacy (VE), defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI: • occurring within 210 days after birth. • occurring within 240 days after birth, if the analysis at 210 days meets efficacy criteria. • occurring within 270 days after birth, if the analysis at 210 days meets efficacy criteria. • occurring within 360 days after birth, if the analysis at 270 days meets efficacy criteria.
Exploratory Objectives – Infant Participants	**Estimands**	**Exploratory Endpoints – Infant Participants**
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI due to RSV.		RSV-positive MA-RTI: • occurring within 90 days after birth. • occurring within 120 days after birth. • occurring within 150 days after birth. • occurring within 180 days after birth. • occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI.		The incidence of all-cause MA-RTIs from vaccination up to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV in infants after 12 months of age.		MA-LRTIs due to RSV occurring 361 to 730 days after birth.

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To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV in infants after 6 months of age.		Severe MA-LRTIs due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV in infants after 6 months of age.		Hospitalization due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI in infants after 6 months of age.		MA-LRTIs due to any cause occurring 181 to 730 days after birth.
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.		RSV subgroup A– and subgroup B–specific MA-LRTI.
To describe the non-RSV infectious etiology of MA-RTI in the study population.		Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits.
To evaluate RSV serum neutralizing titers elicited by RSVpreF and transferred transplacentally.		RSV A and RSV B serum neutralizing titers measured at birth.
To assess the impact of RSVpreF on RSV illness based on socioeconomic factors.		Primary and secondary efficacy by select demographic risk factors (eg, breastfeeding, maternal smoking, number of household members).
To assess the effect of RSVpreF on healthcare utilization.		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.
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.		MA-RTI, MA-LRTI, and severe MA-LRTI due to RSV occurring 0 to 730 days after birth.

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3.2. Maternal Participants

The study objectives and endpoints for maternal participants employ the event definitions in Table 2.

Table 2. Endpoint Events and Definitions in Maternal Participants

Study Endpoints/Assessments	Study Definitions
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 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.

Study Objectives – Maternal Participants

Primary Safety Objective – Maternal Participants	Estimands	Primary Safety Endpoints – Maternal Participants
To describe the safety and tolerability of RSVpreF.	In maternal participants receiving 1 dose of investigational product, the percentage of maternal participants with each safety endpoint in each vaccine group.	The incidence of: • 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 (*Visit 1 through the 6-month-postdelivery study visit*).
Exploratory Objectives – Maternal Participants	**Estimands**	**Exploratory Endpoints – Maternal Participants**
To describe MA-RTI in this study population.		The incidence of all-cause MA-RTIs from vaccination up to 180 days after delivery.
To evaluate the immune responses elicited by RSVpreF.		• RSV A and RSV B serum neutralizing titers and prefusion F IgG titers measured: • before vaccination. • at delivery.

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3.3. Protocol-Defined Efficacy Endpoints

All infant participants experiencing an MA-RTI will have an RTI study visit as detailed in Section 8.1. This protocol will use an independent EAC to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria as summarized in Table 1. Members of this EAC will be blinded to the vaccine assignment to allow for unbiased assessments.

Recognizing that RSV disease is a dynamic illness, sites will be instructed to submit all available source documentation for adjudication from the MA-RTI visit and to record data from the worst day of illness in the electronic case report form (eCRF). The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTI visit, including data collected at the RTI study visit, and all available RSV testing. Further information about the EAC will be detailed in the adjudication charter, including specific descriptions of the scope of its responsibilities and the process and definitions to review and assess study endpoints.

MA-RTI events that are consistent with the clinical and RSV testing endpoint definition and constitute a study endpoint will not be recorded as AEs. For those AEs that are handled as disease-related efficacy endpoints, a data monitoring committee (DMC) will conduct unblinded reviews on a regular basis throughout the trial (see Data Monitoring Committee, Section 9.5.1).

Nonendpoint events (eg, an event that is determined not to be an MA-RTI) must be evaluated for safety reporting as per the protocol requirements. Any AE that is adjudicated by the EAC **to not** meet any endpoint criteria will be reported back to the investigator site of incidence; the investigator at the site must evaluate the event for safety as described in Appendix 2 of this protocol. If the event is classified as serious, the investigator's SAE awareness date in this instance is identified as the date on which the investigator site receives the nonendpoint SAE back from the EAC. Handling these SAEs in this manner will allow Pfizer to meet its sponsor reporting obligations to regulatory authorities upon receipt of such SAEs.

Any events that remain unadjudicated at the annual safety report cutoff date will not be included in the safety tables of the report.

4. STUDY DESIGN

4.1. Overall 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, as well as 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.

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This is an event-driven study with a target of 124 adjudicated (primary-endpoint) cases of MA-LRTI due to RSV at 90 days (meeting the case definition in the per-protocol infant population described in the statistical analysis (Section 9.2). There is no specific case target for the additional primary endpoint of severe MA-LRTI. The total enrollment number of maternal participants may vary depending on the incidence rate of the primary endpoint in the infant participants, true underlying VE, and a potential early stop for efficacy or futility. In the event that efficacy in the infant population is demonstrated at an interim analysis, enrollment of maternal participants may continue in order to obtain safety evaluations in an adequate number of maternal and infant participants to support vaccine registration with national health authorities. Enrollment will be monitored to ensure even distribution of vaccination across gestational age between 24 0/7 and 36 0/7 weeks.

Based on these considerations, and in order to accumulate endpoint cases, 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 the 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 cases of RSV.

Study-eligible pregnant women will be randomized in a 1:1 ratio to receive a single dose of 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).

Once they have provided informed consent, the women will be referred to as "maternal participants" and will be followed from vaccination during pregnancy until 6 months after delivery. Assessments will include parameters to allow descriptions of safety, tolerability, and immunogenicity of the vaccine in maternal participants.

Note: *Maternal participants will include adolescent females who may be referred to as "minors." Information/assessments for minors may require parental/legal guardian awareness/approval per local regulations.*

Infants born to women who receive RSVpreF or placebo in their second or third trimester will be referred to as "infant participants." Infant participants born to women enrolled during the first year of the study will have 6 scheduled study visits during their 24 months of participation, whereas all other infant participants will have up to 4 scheduled study visits during their 12 months of participation. 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. For infant participants enrolled during the first year of the study, the extended 12-month study duration will involve longer-term RTI surveillance and safety oversight to address safety and the possibility of conferred enhanced protection (antibody persistence) during a second RSV season.

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All MA-RTIs meeting the protocol definition for a potential study endpoint will be adjudicated by an independent adjudication committee. In addition, this study will use an E-DMC to monitor vaccine safety and efficacy and study futility.

4.1.1. Approximate Duration of Participation for Each Participant

Pregnant women will participate in the study from enrollment during their pregnancy, and for approximately 6 months after delivery of their infants. The total duration will be up to approximately 10 months, depending on GA at the time of vaccination and when the infant is actually born.

All eligible infant participants born to enrolled maternal participants during the first year of the study will participate in the study from the time of birth and will be followed for up to 24 months for RSV surveillance and safety for the secondary and exploratory endpoints of the study. All other infants will participate from the time of birth and for at least 12 months after birth.

4.1.2. Approximate Number of Participants

Healthy pregnant women will be randomly assigned to a study intervention. It was anticipated that approximately 6900 mother-infant pairs would be needed to accumulate 124 per-protocol cases as defined in Section 9.2 of the protocol 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 cases of RSV. Enrollment will be monitored to ensure that participants will be recruited from both the northern and southern hemispheres. Enrollment may vary depending on the incidence in the placebo group, the true underlying VE, the dropout rate, and a potential early stop for VE or futility.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1.

4.3. Justification for Dose

The final dose and formulation of RSVpreF selected for use in this study is based on the safety and immunogenicity data from the ongoing C3671003 maternal immunization study (*A Phase 2b, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants; ClinicalTrials.gov identifier: NCT04032093*) and the first-in-human (FIH) study C3671001.

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The FIH study was designed to describe the safety, tolerability, and immunogenicity of 6 RSVpreF candidates with bivalent formulations (RSV A and B) at 3 escalating dose levels of 60 µg (30 µg A and 30 µg B), 120 µg (60 µg A and 60 µg B), and 240 µg (120 µg A and 120 µg B) of the RSV prefusion F antigen, with or without $Al(OH)_3$, when administered alone or concomitantly with seasonal inactivated influenza vaccine. The study utilizes a sentinel cohort (N=168; Phase 1) and an expanded cohort (N=1014; Phase 2). Nonpregnant female and male study participants of 2 age groups, 18 through 49 years of age and 50 through 85 years of age, were enrolled into both cohorts. The age groups are being run in parallel.

An interim analysis of participants 18 through 49 years of age, including safety and tolerability (n=533) and immunogenicity (n=513) data up to 1 month after vaccination in the expanded cohort and additional immunogenicity data up to 3 months after vaccination in the sentinel cohort, has shown the RSVpreF candidate to be immunogenic and well tolerated.

Local reactions and systemic events were noted to be predominantly mild or moderate across all doses and formulations, which is consistent with the current safety profile. The safety results from this planned interim analysis of healthy male and nonpregnant female participants 18 through 49 years of age are consistent with those from the sentinel-cohort analysis and indicate that RSVpreF has an acceptable safety profile and is well tolerated.

The immunogenicity results showed that RSVpreF elicited neutralizing titer geometric mean fold rises (GMFRs) of 10 to 20, 1 month after vaccination, depending on the formulation. Similarly, across all dose levels, with and without $Al(OH)_3$, RSVpreF elicited high 1-month-postvaccination RSV A and RSV B neutralizing GMTs. Overall, RSVpreF elicited anti–prefusion F immunoglobulin G1 (IgG1) responses that paralleled the elicited RSV-neutralizing responses. The ratio of RSV 50% neutralizing antibody titer GMFRs to prefusion RSV F binding IgG1 titer GMFRs (calculated with combined data for subgroups A and B) for the sentinel and expanded 18 through 49 years of age cohorts combined ranged from 0.62 to 0.76. The IgG1 and neutralization responses were similar in antigen-level dose response, in equivalence of RSV A titer GMFRs to RSV B titer GMFRs, and in a lack of effect of $Al(OH)_3$.

Safety data for 403 mother/infant pairs, from maternal participants through 1 month after maternal vaccination and for their infants from birth through the first month of life, in Study C3671003 provide further evidence of the safety of RSVpreF in maternal vaccine recipients, and initial evidence of the safety of maternal vaccination with RSVpreF for the infant. In maternal participants, solicited symptoms were generally mild to moderate in intensity and of short duration. Unsolicited AEs were consistent with anticipated events in this participant population and did not indicate any differences between RSVpreF and control recipients. No differences in pregnancy (eg, reports of preterm delivery or obstetric complications) and birth outcomes (eg, reports of respiratory distress at delivery or presence of congenital anomalies) were observed between RSVpreF and control recipients. No differences in the number or types of AEs reported were observed between infants born to mothers receiving RSVpreF and those receiving placebo in the first month of life.

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The high ratio of RSV-neutralizing antibody titer GMFRs to prefusion F–binding titer GMFRs elicited by Pfizer's RSVpreF candidate indicates that most of the elicited antibody can neutralize the virus. It is assumed that this reflects the ability of the antibodies to prevent RSV disease in immunized participants and, in the case of maternal immunization, prevent disease in their infants.

The primary mechanism for protection of infants by the RSV maternal vaccine is neutralization of the virus by transplacentally transferred antibody, which is increased by immunization. Maternal antibody decays exponentially in infants. Therefore, it is anticipated that higher titers of transferred neutralizing antibodies will provide greater levels and durations of infant protection. Results from the C3671001 FIH trial were used to determine the doses and formulations that are currently under investigation in the Phase 2b maternal immunization study: 120 µg or 240 µg of RSVpreF with or without $Al(OH)_3$. These doses are expected to provide the greatest potential level of transplacental antibody transfer to infants and, therefore, the greatest potential benefit. The dose and formulation of RSVpreF for the Phase 3 study was determined by the evaluation of the 1-month safety, tolerability, and immunogenicity results from the C3671003 maternal Phase 2b trial, including infant RSV-neutralizing titers at birth.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

The end of the study is defined as the date of the last visit of the last infant participant in the study. The study may also be terminated earlier for efficacy or futility as described in Section 9.5.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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5.1. Inclusion Criteria

5.1.1. Inclusion Criteria – Maternal Participants

Participants are eligible to be included in the study only if all of the following criteria apply (refer to the investigator site file [ISF] for further eligibility details regarding region-specific timing of vaccination with respect to RSV seasonality and maternal gestational age at vaccination):

Note: In countries/locales where study procedures used to determine eligibility criteria (eg, ultrasound examination, human immunodeficiency virus [HIV] testing, syphilis testing) are not performed as part of routine prenatal care, they must be performed as part of this clinical trial and reviewed by the investigator or qualified designee within 28 days prior to randomization. **Maternal participants must provide informed consent prior to performing any procedures, including those that are being done exclusively to meet study eligibility criteria.**

Note: Country-specific modifications associated with the study eligibility criteria are documented in Appendix 7, Appendix 8, and Appendix 9.

Age and Sex:

1. Healthy women ≤49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications.

   Note: GA must be based upon 1 of the following composite criteria based on timing and availability of data on the last menstrual period (LMP) and an ultrasound examination performed in the first or second trimester.[35] The earliest ultrasound data available during the current pregnancy should be used. In countries where the routine practice is for the GA determination to be based upon the first trimester ultrasound examination alone, without the LMP, this routine practice will be accepted.

   a. **First-trimester data available** (data obtained at ≤13 6/7 weeks):

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

If there is a discrepancy of >5 days between the LMP-determined GA and an ultrasound result at ≤8 6/7 weeks OR the LMP is uncertain/unknown, then the GA should be determined using the first-trimester ultrasound result.

If there is a discrepancy of >7 days between the LMP-determined GA and an ultrasound result at 9 0/7 to 13 6/7 weeks OR the LMP is uncertain/unknown, then the GA should be determined using the first-trimester ultrasound result.

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b. **Second-trimester data available** (data obtained at 14 0/7 to 27 6/7 weeks):

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

If there is a discrepancy of >7 days between the LMP-determined GA and the ultrasound result at 14 0/7 to 15 6/7 weeks OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound result.

If there is a discrepancy of >10 days between the LMP-determined GA and the ultrasound result at 16 0/7 to 21 6/7 weeks OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound result.

If there is a discrepancy of >14 days between the LMP-determined GA and the ultrasound result at 22 0/7 to 27 6/7 weeks OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound result.

Type of Participant and Disease Characteristics:

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

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

4. Had a fetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed.

5. Determined by medical history, physical examination, and clinical judgment to be appropriate for inclusion in the study.

6. Documented negative HIV antibody test, syphilis test, and hepatitis B virus (HBV) surface antigen test during this pregnancy and prior to randomization (Visit 1).

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

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

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

Informed Consent:

10. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol **OR**

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If the maternal participant is illiterate, a thumbprinted informed consent must be obtained, which must be signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant has been informed of all pertinent aspects of the study.

5.1.2. Inclusion Criteria – Infant Participants

1. Evidence of a signed and dated ICD signed by the parent(s)/legal guardian(s) **OR**

   If the infant participant's maternal participant/parent(s)/legal guardian(s) is illiterate, a thumbprinted informed consent must have been obtained, which must have been signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant/parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study for herself (maternal participant) and her fetus/infant prior to taking part in the study.

   Note: Informed consent will be obtained from the father of the fetus/infant if mandated by local requirements.

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

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria – Maternal Participants

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

Weight:

1. Prepregnancy body mass index (BMI) of >40 kg/m^2. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used.

Medical Conditions:

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

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

4. Current pregnancy resulting from in vitro fertilization. *Participants known to have used clomiphene citrate and/or letrozole with or without intrauterine insemination (IUI) are permitted.*

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5. Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:

    - Preeclampsia, eclampsia, or uncontrolled gestational hypertension.
    - Placental abnormality.
    - Polyhydramnios or oligohydramnios.
    - Significant bleeding or blood clotting disorder.
    - Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism. This also includes disorders of glucose intolerance (eg, diabetes mellitus type 1 or 2) antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent.
    - Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth.

6. Prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:

    - Prior preterm delivery ≤34 weeks' gestation.
    - Prior stillbirth or neonatal death.
    - Previous infant with a known genetic disorder or significant congenital anomaly.

7. Major illness of the maternal participant or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the maternal or infant participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response (includes positive serologic testing for regional endemic conditions assessed during routine maternal care, as per local standards of care and obstetric recommendations).

8. Congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrollment.

9. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

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Prior/Concomitant Therapy:

10. Participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation.

11. Receipt of monoclonal antibodies within the year prior to enrollment or the use of systemic corticosteroids for >14 days within 28 days prior to study enrollment. *Permitted treatments include the receipt of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies, prednisone doses of <20 mg/day for ≤14 days and, inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids.*

12. Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales.

13. Receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (eg, RhoGAM), which can be given at any time.

Prior/Concurrent Clinical Study Experience:

14. Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation. **Note:** *Licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary, or emergency use will not be prohibited during the course of this study.*

Diagnostic Assessments:

Not applicable.

Other Exclusions:

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

16. Participants who are breastfeeding at the time of enrollment.

5.2.2. Exclusion Criteria – Infant Participants

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

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5.2.3. Temporary Vaccination Delay Criteria – Maternal Participants

The following conditions are temporary or self-limiting and a maternal participant may be vaccinated once the condition(s) has/have resolved and if no other exclusion criteria are met. The prevaccination blood draw and vaccination should take place on the same day. In the event that this is not possible, the prevaccination blood draw is also permissible within 7 days before the vaccination visit.

- Current febrile illness (body temperature ≥38°C [≥100.4°F]) or other acute illness within 48 hours before investigational product administration.
- Diagnosed malaria within the last 7 days prior to investigational product administration.
- Receipt of any inactivated vaccine (including licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary or emergency use) within 14 days or any live vaccine within 28 days before investigational product administration.
- If systemic corticosteroids (equivalent of ≥20 mg/day of prednisone) have been administered short term (≤14 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

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6.1. Study Intervention(s) Administered

For this study, the investigational product(s) are RSVpreF and placebo (lyophile match).

6.1.1. Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The RSV vaccine will be 120 µg of the RSV prefusion F antigen. The vaccine is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The vaccine will be reconstituted by a diluent consisting of sterile water in a prefilled syringe (PFS). The lyophilized vaccine contains excipients that, after reconstitution, will yield a solution as detailed in the IB.

The fill volume of the vaccine vial and diluent PFS are designed such that the intended vaccine dose is delivered by injecting the entire contents of the syringe.

6.1.2. Placebo

Placebo will be a lyophile match to the vaccine, which will consist of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients.

The physical appearance of the reconstituted RSVpreF and placebo will be matched, and the study will be conducted in a double-blinded manner.

The fill volume of the placebo vial and diluent PFS is designed such that the intended placebo dose is delivered by injecting the entire contents of the syringe.

Placebo will be provided by the sponsor to each study site. The placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

6.1.3. Administration

Maternal participants will receive 1 dose of investigational product at the vaccination visit (Day 1) in accordance with the study's SoA. The investigational product will be administered intramuscularly by injecting the entire contents of the syringe into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Investigational product administration will be performed by appropriately designated study staff at the investigator site.

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

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

Investigational product administration details will be recorded on the case report form (CRF).

6.1.4. Medical Devices

In this study, medical devices being deployed are for the reconstitution diluent for the investigational product (RSV vaccine or placebo). The investigational product supplies are provided in a kit that contains the investigational product (RSV vaccine or placebo lyophilized powder in a vial), a prefilled syringe containing sterile water, and a vial adapter.

Instructions for medical device use are provided in the investigational product manual (IP manual).

Medical device deficiencies, including those resulting from malfunctions of the device, must be detected, documented, and reported by the study personnel throughout the study.

Please refer to Section 8.3.9 for details.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

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

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. See the IP manual for storage conditions of the study intervention once reconstituted.

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

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

Refer to the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Investigational product and placebo will be prepared by qualified site personnel according to the IP manual. The investigational product will be administered only to maternal participants who are blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Blinding of Study Site Personnel

This study is a double-blinded study, as the physical appearance of RSVpreF and placebo will be matched. The maternal participant, her parent(s)/legal guardian (if a minor), investigator, study coordinator, and all site staff will be blinded.

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Please refer to the IP manual for further details.

6.3.2. Blinding of the Sponsor

The sponsor study team members will be blinded throughout the study to the vaccine assignments of all participants enrolled in the study.

Laboratory personnel performing the serology and virology assays will remain blinded to vaccine assigned/received throughout the study.

6.3.3. Allocation to Investigational Product

Allocation (randomization) of maternal participants to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the maternal participant number. The site personnel will then be provided with a vaccine assignment, randomization number, and dispensable unit (DU) or container number as investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the maternal participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Note: Maternal participants will be randomized to a vaccine group as described above. The infants of the maternal participants will be manually assigned an infant participant number at birth.

Investigational product will be dispensed and administered at study Visit 1 summarized in the SoA.

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

Maternal participants will be assigned to receive investigational product according to the randomization scheme. Investigators will remain blinded to the investigational product assigned to each maternal participant throughout the course of the study.

6.3.4. Breaking the Blind

The study will be maternal participant and investigator blinded.

At the initiation of the study, the investigator will be instructed on the method for breaking the blind for an individual participant. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. The investigators should make every attempt to contact a member of the sponsor's study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

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

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

6.5.1. Prohibited Concomitant Vaccinations and Treatments – Maternal Participants

- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study. Note: COVID-19 vaccines authorized for temporary, or emergency use will not be prohibited during the course of this study.

- Receipt of blood/plasma products or Ig, from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (eg, RhoGAM), which can be given at any time.

- Immunosuppressive therapy is prohibited during the course of the study.

- Nonstudy vaccines may not be given concomitantly with the investigational product or within 7 days after investigational product administration (Day 1 to Day 7), except if medically necessary (eg, during an outbreak or pandemic situation).

- Note: Licensed vaccines containing pertussis (including Tdap) may not be coadministered with the investigational product or given within 14 days after investigational product administration (Day 1 to Day 14), except if medically necessary (eg, during an outbreak- or pandemic-related situation).

6.5.2. Permitted Concomitant Vaccinations and Treatments – Maternal Participants

- Licensed vaccines (including influenza vaccine, tetanus toxoid, tetanus diphtheria vaccines, licensed COVID-19 vaccines, and COVID-19 vaccines authorized for temporary or emergency use) may be given during the study starting 7 days after investigational product administration (Day 8), with the exception of licensed vaccines containing pertussis (including Tdap), which may be given starting 14 days after investigational product administration (Day 15) as detailed in Section 6.5.1.

- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. Short-term systemic corticosteroid (equivalent of <20 mg/day of prednisone) use for ≤14 days prior to the administration of investigational product is permitted.

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during participant participation in the study.

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6.5.3. Recording Nonstudy Vaccinations and Concomitant Medications – Maternal Participants

The following vaccinations and treatments for maternal participants would require reporting in the CRF during the study:

- Details of any vaccinations given at any time during the pregnancy through the final study visit will be collected and recorded in the CRF.

- Details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given to the maternal participant at any time during the pregnancy or during the study will be collected and recorded in the CRF.

- Any **prescribed** medications taken to treat medically attended respiratory illnesses from enrollment until the final study visit will be recorded in the CRF.

Concomitant medications not meeting the criteria above will be assessed but not documented on the CRF.

6.5.4. Prohibited Concomitant Vaccinations and Treatments – Infant Participants

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

6.5.5. Permitted Concomitant Vaccinations and Treatments – Infant Participants

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

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

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

6.5.6. Recording Nonstudy Vaccinations and Concomitant Medications – Infant Participants

The following CRF reporting guidelines are applicable to treatments given to infant participants during the study:

- Details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, hepatitis B immune globulin (HBIG)]) or blood products (eg, whole blood, packed cells) given to the infant participant will be collected from the time of birth until the final study visit and recorded in the CRF.

- Any **prescribed** medication taken to treat medically attended respiratory illnesses from the time of birth until the final visit.

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- Details of IV fluids given during an MA-RTI will be collected and recorded in the CRF.

6.6. Dose Modification

Dose modification is not applicable in this study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Discontinuation of study intervention is not applicable in this study.

7.2. Participant Discontinuation/Withdrawal From the Study

A maternal participant may withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. An infant participant may withdraw from the study at any time at the request of his or her parent(s) and/or legal guardian(s) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The participants, or, if appropriate, their parent(s) and/or legal guardian(s), should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued from the study at that time.

If a maternal participant withdraws from the study, she may request destruction of any remaining samples taken and not tested, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses. If an infant participant is withdrawn from the study, his or her parent(s) and/or legal guardian(s) may request destruction of any remaining samples, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records and notify the sponsor accordingly.

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

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Vaccine SAE Reporting Form.

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

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Participants who withdraw after randomization will not be replaced.

7.3. Withdrawal of Consent

Maternal participants and parent(s)/legal guardian(s) of infant participants born to maternal participants who request to withdraw consent from any further study contact or with persons previously authorized by the participant to provide this information should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from study procedures and/or postvaccination study follow-up. If the participant (maternal or infant) only withdraws from a study procedure, safety information should be completed until the end of the study, unless consent for further contact has been withdrawn. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

The regulatory and ethical considerations for this study, including the informed consent process, are summarized in Section 10.1.1 and Section 10.1.3.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

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

    - Should the participant or parent(s) and/or legal guardian(s) continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

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8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Efficacy Assessments – Infant Participants

MA-RTIs in the infant participant will be identified from 72 hours after the infant's delivery until the end of the infant's participation in the study. If the infant participant meets any RTI criteria listed below that require a visit by or a visit to an HCP (outpatient or inpatient visit, emergency room, urgent care, or scheduled home visit), an RTI study visit by the study staff will be required (see Section 8.11.7).

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The RTI criteria are if the infant experiences 1 or more of the following respiratory signs or 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 due to respiratory symptoms
- Apnea
- Any other respiratory symptom of concern

Evaluation of these MA-RTI events will be based on predefined clinical signs and symptoms and testing criteria (shown in Table 1) obtained at the medically attended visit with the healthcare provider and/or the study visit. These events will be assessed and confirmed to be contributing to the study endpoints by an independent EAC as per the protocol.

8.1.1.1. Midturbinate Nasal Swab Collection and Testing Requirements for Endpoint Confirmation – Infant Participants

Midturbinate nasal swabs will be collected for RSV analyses from infant participants at each RTI study visit during the RSV surveillance period from birth until Visit 3, and for all hospitalizations due to an RTI and severe cases of MA-LRTI during the RTI surveillance period from Visit 3 until the end of the study (see Section 1.2.4.1 and Table 1). The swabs will be sent to Pfizer for centralized reverse transcription–polymerase chain reaction (RT-PCR) testing.

RSV testing performed locally as part of routine care will be considered valid when analyzed under the following conditions:

- Nucleic acid amplification technology (NAAT)-based test result positive for RSV was obtained using an FDA-cleared assay.

  AND

- NAAT-based test result was obtained in a laboratory that is currently Clinical Laboratory Improvement Amendments (CLIA)-certified or has the equivalent US certification/accreditation (eg, College of American Pathologists [CAP]) or the equivalent ex-US certification as outlined in the adjudication charter.

Note: Rapid antigen-based test results will not be considered for endpoint assessment.

Study samples should be collected as close to the medical visit as possible and preferably within 72 hours of the MA-RTI visit. Study samples positive for RSV by RT-PCR as defined above will count toward the endpoint definition when collected for up to 10 days

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after the MA-RTI, where Day 1 is the day of the MA-RTI visit. These results will be used for MA-RTI endpoint definition and confirmation as detailed in Table 1.

8.1.1.2. Events for Adjudication and Submission Guidance – Infant Participants

To maintain scientific integrity, this protocol will use an EAC for the adjudication of all efficacy endpoints as summarized below. The EAC will remain blinded to the maternal participants' vaccine assignments, and the EAC's assessment of these events will represent the final confirmed endpoint classification of the event.

The efficacy-related events for adjudication include all MA-RTI events. The study definitions for endpoint events and the MA-RTI adjudication criteria for the EAC, including roles and responsibilities, are specified in the endpoint adjudication committee charter (EACC).

The identification of an MA-RTI will be made by the investigational site and communicated to Pfizer or its designee. However, these MA-RTI events may also be identified by Pfizer or its designee during the review of clinical data listings or by site monitors during routine monitoring of the infant participants' study records. Pfizer or its designee will notify the investigational site of any events identified during this process.

The EAC is responsible for adjudicating whether MA-RTI events fulfill the protocol-defined clinical criteria as a primary endpoint, whether the event was due to RSV based on confirmatory testing, and the severity of the illness (eg, MA-RTI, MA-LRTI, or severe MA-LRTI). The EAC will adjudicate all RSV-positive MA-RTI cases through the active follow-up period including all cases occurring up to 180 days after birth. The EAC will adjudicate severe manifestations of RSV: all RSV-associated cases of hospitalization and severe MA-LRTI. All deaths during the study are to be reported to Pfizer Safety upon awareness.

The Pfizer study team or designee will provide a listing of specific documents needed to support endpoint adjudication by the EAC. These documents will be detailed in the EACC and the ISF. Obtaining and submitting the documentation, including results of local testing for RSV, will be the responsibility of the investigational site. Documentation will vary based on the potential endpoint requiring adjudication and may include (but not be limited to) emergency room visit records, hospital discharge summaries, clinic and/or progress notes, diagnostic tests, pathology reports, autopsy reports, and death certificate information, as applicable.

Pfizer may request that additional cases of interest be reported to the committee in addition to those listed above, including cases in which RSV testing is indeterminant or otherwise unclear. Cases that are determined to be RSV positive using non–NAAT-based clinical testing can be adjudicated, explored, and summarized descriptively.

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8.1.2. Exploratory Efficacy Assessments – Maternal Participants

An MA-RTI will be identified from vaccination until the end of the study and will contribute to an exploratory endpoint for maternal participants. The definition and assessment criteria as described in Section 8.10.6 include a visit by or to a healthcare provider (outpatient or inpatient visit, emergency room, urgent care, or home visit) for any symptoms in the RTI criteria as detailed in Table 2.

The maternal participant or her parent(s)/legal guardian (if a minor) should contact the study staff immediately but no later than the next scheduled visit to report RTI signs and symptoms for which she sought medical attention. The procedures as detailed in Section 1.2.3.1 and Section 8.10.6 will be required to capture the event in the CRF.

8.1.3. Efficacy Endpoints and Safety Reporting Requirements – Maternal and Infant Participants

Infant MA-RTI events that are consistent with the clinical and endpoint definitions for infant participants should not be recorded as AEs. These data will be captured as efficacy assessment data only, as these are expected endpoints.

For maternal participants, MA-RTI events that are consistent with the clinical and endpoint definition will be captured as detailed in Section 8.1.2 and will not be recorded as AEs.

Any event that the investigator has judged to have a causal relationship with the investigational product or to have resulted in death MUST be reported to Pfizer Safety as described in Appendix 2, even if that event is a component of an endpoint.

8.1.4. Immunogenicity Assessments

8.1.4.1. Total Volume of Blood Collected – Maternal Participants

The total volume of blood collected for antibody assessment over the course of the study will be approximately 30 mL (~15 mL/visit).

8.1.4.2. Total Volume of Blood Collected – Infant Participants

Blood samples will be collected according to the directive 2001/20/EC: Ethical Consideration for Clinical Trials Performed in Children.[36]

All infants will have a cord blood sample collected at birth. The cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been clamped and cut. Blood should be collected as soon as feasible after birth to minimize coagulation and maximize volume. **The total volume of cord blood to be collected for antibody assessment in this study will be 10 mL**.

If cord blood is unavailable, a blood sample may be collected from the infant participant up to 7 days after birth but **preferably within 24 hours after birth.** The infant's weight must be used to determine the volume of blood that can be collected (see Table 3).

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A blood sample will be collected from the infant participant only if a cord sample is not obtained. In the event that a sample is collected, the volume of blood will vary depending on the infant's weight.

The maximum volume of blood collected from the infant in the absence of cord blood will be no more than 5 mL.

Table 3. Guideline for Infant Blood Draw if Cord Blood Sample Was Not Obtained

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

8.1.4.3. RSV Vaccine Antibody Testing – Maternal and Infant Participants

Maternal sera (prevaccination/time of delivery) and infant cord blood collected will be assayed for RSV A and RSV B serum neutralizing titers and anti-RSV prefusion F IgG levels. Maternal sera collected may be tested for Ig levels against nonvaccine RSV antigens to assess natural RSV exposure.

RSV A and RSV B serum neutralizing titers will be determined and reported as the neutralizing titer. IgG levels will be determined against both RSV A and RSV B prefusion F antigens in a direct-binding Luminex immunoassay (dLIA) and reported as an anti–prefusion F IgG level.

Sample collection, processing, storage, and shipping information can be found in the ISF or equivalent manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

8.1.4.4. Exploratory Assays, Including Immunogenicity Assessments and Assay Development – Maternal and Infant Participants

Samples remaining after completion of the planned assays from blood draws or infant respiratory nasal swab specimens taken throughout the study may be used for additional vaccine and infectious disease related research. Samples may also be used for assay development, standardization, qualification, and validation. This work is critical in the development, qualification, and validation of serological assays and is required by regulatory authorities for their use in the licensure of a vaccine.

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8.1.4.5. Respiratory Pathogens – Infant Participants

Midturbinate nasal swabs will be collected from infant participants following **any MA-RTI visit** during the RSV surveillance period from birth until Visit 3, and for **all hospitalizations due to an RTI and severe cases of MA-LRTI** during the RTI surveillance period from Visit 3 until the end of the study (see Section 1.2.4.1 and Table 1).

Samples will be analyzed for RSV A, RSV B, and other respiratory pathogens by polymerase chain reaction (PCR)-based assays at a central laboratory. Additional exploratory analyses may also be performed.

Sample collection, processing, storage, and shipping information can be found in the ISF or equivalent manual. All assays will be performed by Pfizer and/or at a facility designated by Pfizer.

8.1.4.6. Biological Samples – Maternal and Infant Participants

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

The maternal participant may request that her (or her infant's) samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained, and no testing of the maternal and infant participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Safety parameters will be assessed as described in the SoA and below for both maternal and infant participants.

8.2.1. Participant Electronic Diary – Maternal Participants

All maternal participants vaccinated in the study will be observed for at least 30 minutes after investigational product administration for any acute reactions. For all maternal participants, prespecified local reactions and systemic events will be collected for 7 days after vaccination.

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Maternal participants will be required to use an electronic diary (e-diary), installed on a provisioned device or as an application on a personal device, and will be asked to monitor and record local reactions, systemic events, and temperature each evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). Prior to vaccination, a baseline assessment of prespecified systemic events will be recorded in the e-diary.

The e-diary allows recording of these assessments only within a fixed time window each day, thus providing the accurate representation of the maternal participant's experience at that time.

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

Data on local reactions, systemic events, and temperature recorded in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be recorded by the investigator in the CRF, except the following conditions:

- If a maternal participant withdraws because of prompted events recorded in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

- The investigator or designee must obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

Investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate maternal participant compliance and as part of the ongoing safety review. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.2.1.1 and Section 8.2.1.2.

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8.2.1.1. Local Reactions – Maternal Participants

Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), the maternal participants or her parent(s)/legal guardian (if a minor)/study staff member/field worker will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary or appropriate device, in the evening or daily based on local practice.

Redness and swelling will be measured by the maternal participant/study staff/field worker 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 maternal participant with severe redness, swelling, or pain at the injection site will be prompted to contact the investigator to perform an unscheduled visit to assess the reaction or will be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant or her parent(s)/legal guardian (if a minor).

Only an investigator or a qualified designee 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. If a maternal participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. A Grade 4 reaction will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.2.4).

The site staff/field worker will educate the maternal participant and her parent(s)/legal guardian (if a minor) regarding signs and symptoms that would prompt site contact.

If a local reaction persists beyond the end of the e-diary period, the maternal participant or her parent(s)/legal guardian (if a minor) will be requested to report that information and/or any new AEs that develop to the investigator, or the study staff/field worker will continue to call or visit the maternal participant to assess and record the information until resolution, as per local practice. The investigator will enter this additional information in the maternal participant's source notes and CRF.

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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 or qualified designee 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 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.4.

8.2.1.2. Systemic Events – Maternal Participants

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. Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), maternal participants or their parent(s)/legal guardian (if a minor) will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening or, based on local practice in certain countries/locales, a study staff member/field worker will call or visit maternal participants daily after vaccination to assess the presence of systemic events each day (beginning in the morning) for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). The study staff member/field worker will record the symptoms in the e-diary daily. The symptoms will be assessed by the maternal participant according to the grading scale in Table 5. Maternal participants and their parent(s)/legal guardian (if a minor) will also be instructed to contact site staff if they visit the emergency room or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain within 7 days after vaccination. Based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant or her parent(s)/legal guardian (if a minor). The study staff/field worker may also contact the maternal participant or her parent(s)/legal guardian (if a minor) to obtain additional information on events entered into the e-diary.

Only an investigator or qualified designee 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

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the maternal participant. If a maternal participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.2.4).

Further, if a systemic event persists beyond the end of the e-diary period, the maternal participant or her parent(s)/legal guardian (if a minor) will be requested to report that information and/or any new AEs that develop to the investigator, or the study staff/field worker will continue to call or visit the maternal participant to assess and record the information until resolution, as per local practice. The investigator will enter this additional information in the maternal participant's source notes and 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 or qualified designee 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 systemic reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.4.

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8.2.1.3. Temperature – Maternal Participants

A digital thermometer will be given to the maternal participant with instructions on how to measure oral temperature at home in degrees Celsius. Temperature will be collected in the evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) and at any time during the 7 days following vaccination that fever is suspected. Similarly, based on local practice in certain countries/locales, the study staff/field worker will call or visit maternal participants daily for 6 days after vaccination (Day 2 through Day 7, where Day 1 is the day of vaccination) to collect the temperature.

Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary, where possible. In certain countries/locales, if a temperature of ≥38.0°C (≥100.4°F) is recorded for a maternal participant during the collection of diary events after vaccination, the study staff/field worker will perform a rapid test for malaria as per local practice.

In the event of a fever on the last day the diary was completed, temperature will be measured daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F]) in order to collect a stop date in the CRF.

A maternal participant with a fever >38.9°C (>102.0°F) will be prompted to contact the investigator. Based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns, as applicable. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant or her parent(s)/legal guardian (if a minor). The investigator or qualified designee will assess the fever and perform an unscheduled visit as appropriate.

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.

Temperature will be measured and recorded to 1 decimal place and then categorized during analysis as mild, moderate, or severe based on the intensity grading scale provided in Table 6.

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Table 6. Ranges for Fever

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fever	≥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 case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.4.

8.2.2. Clinical Safety Laboratory Assessments – Maternal and Infant Participants

There are no protocol-required laboratory assessments.

8.3. Adverse Events and Serious Adverse Events

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 4. Device deficiencies are covered in Section 8.3.9.

AEs will be reported by the maternal participant/parent(s)/legal guardian(s).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or caused the participant to discontinue from the study (see Section 7).

Each maternal participant or her parent(s)/legal guardian (if a minor) and parent/legal guardian/legally authorized representative of an infant participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

Maternal Participants

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 and 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.

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In this study, the investigator and site staff will ensure the active elicitation and collection of safety events as detailed below:

- The active collection period for nonserious AEs begins once informed consent has been provided and continues 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 AEs/SAEs 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 or to have resulted in death as detailed in Section 8.1.2 and Section 8.1.3.

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

Infant Participants

For the infant participant, the time period for actively eliciting and collecting safety events is detailed below:

- The active collection period for 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 AEs/SAEs 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 the event resulted in death. See Section 8.1 for the reporting procedures for efficacy-related endpoints. Note: Details of the MA-RTI visit should be recorded in the eCRF.
- 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.

For Both Maternal and Infant Participants

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

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For maternal participants, and parent(s)/legal guardian(s) of infant participants born to maternal participants, who withdraw from the study and withdraw consent for the collection of future information, the active collection period ends when consent is withdrawn.

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the Vaccine SAE Reporting Form, immediately upon awareness and under no circumstances should this exceed 24 hours.

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

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

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

The same is applied for those SAEs after the active collection period has ended, should they occur to the fetus. In addition, infant deaths that occur after 12 months of age should be reported as SAEs when the investigator believes the SAE or death has at least a reasonable possibility of being related to investigational product.

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

*Further guidance on the identification and classification of congenital anomalies (structural and developmental), including genetic syndromes for this study, can be found in the ISF and is based on the Metropolitan Atlanta Congenital Defects Program.[37]

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8.3.1.2. Recording Nonserious AEs and SAEs in the CRF

All AEs/SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed, and all spontaneously reported AEs and SAEs reported by the participant, or her parent(s)/legal guardian (if a minor) and parent(s)/legal guardian(s) of infant participants born to maternal participants.

The investigator obtains general information on the pregnancy and its outcome for all study participants. The investigator will follow the pregnancy until completion (or until pregnancy termination). In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, stillbirth, neonatal death, defined as those deaths that occur within 1 month after birth; or congenital anomaly* [in a live-born baby, a stillbirth, or a neonatal death]), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

*Further guidance on the identification and classification of congenital anomalies (structural and developmental), including genetic syndromes for this study, can be found in the ISF and is based on the Metropolitan Atlanta Congenital Defects Program.[37]

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4).

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

Potential efficacy endpoints on this study as defined in Section 8.1 will be excluded from the standard SAE reporting process unless deemed possibly related to investigational product.

8.3.5. Additional Exposure Scenarios That May Result From the Exposure to the Investigational Product

8.3.5.1. Exposure During Breastfeeding

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

Scenarios of exposure during breastfeeding for infants not delivered during the study must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the Vaccine SAE Reporting Form. An exposure-during-breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

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8.3.5.2. Occupational Exposure

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

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

In addition, the scenarios below describe environmental exposures that could lead to an exposure during pregnancy (EDP):

- A female becomes or is found to be pregnant, having been exposed (eg, because of environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after being exposed to the investigational product;

- A male has been exposed (eg, because of environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the Vaccine SAE Reporting Form and the Exposure During Pregnancy Supplemental Form, as applicable, regardless of whether there is an associated SAE. In the event of an EDP, the information submitted should include the anticipated date of delivery. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs are as follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until

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completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

This section provides information on adverse events of special interest (AESIs) that may be detected during the study.

For infant participants[38]:

- Preterm birth (born at <37 weeks' gestation)
- Birth weight 1001 to 2500 g
- Developmental delay*
- **Positive viral (PCR or antigen-based) testing** for SARS-CoV-2, when not reported during a MA-RTI visit, should be reported as SARS-CoV-2 test positive

The following AESIs are to be reported as SAEs:

- Extremely preterm birth (<28 weeks)
- Extremely low birth weight (≤1000 g)

For maternal participants:

- Preterm delivery
- **Positive viral (PCR or antigen-based) testing** for SARS-CoV-2, when not reported during a MA-RTI visit, should be reported as SARS-CoV-2 test positive

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through Section 8.3.4 except the active collection period for AESIs is from the signing of the ICD until the end of the study for maternal participants and from birth until the end of the study for infant participants.

Notes: An AESI that is recorded as an SAE must be reported using the Vaccine SAE Reporting Form.

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*Developmental delay is to be assessed by clinical expertise using local guidelines for standard of care. Events identified as both an AESI and an NDCMC should be reported as an AESI in the CRF.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purposes of administering the investigational product. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 4.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 2 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 4.

8.3.9.2. Follow-up of Medical Device Deficiencies

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency.

Information will be provided to the sponsor as described in the IP manual.

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Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Section 8.3.1.1 and Section 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration by an incorrect route;

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- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE**.

8.4. Treatment of Overdose

For this study, any additional dose of investigational product will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

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

No interruptions or dose modifications will be made in this study.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

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8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics will be evaluated in exploratory analyses assessing vaccine impact on healthcare resource utilization parameters evaluated during study visits, 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.

8.10. Procedures – Maternal Participants

8.10.1. Screening and Vaccination Visit (Clinic; 28 Days Prior to Vaccination to Day 1 – Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant or their parent(s)/legal guardian (if a minor). Each signature on the ICD must be personally dated by the signatory.

Maternal participants who might be illiterate must thumbprint the ICD and it must be signed and dated by an impartial witness who was present throughout the entire informed consent process before performing any study-related procedures.

The investigator or his or her designee will also sign and date the ICD. A copy of the signed/thumbprinted and dated ICD must be given to the maternal participant and her parent(s)/legal guardian (if a minor). **The source data must reflect that the informed consent was obtained before participation in the study.**

If the maternal participant is found ineligible for the study based on a full assessment of inclusion and exclusion criteria, the investigator may advise the participant and her parent(s)/legal guardian (if a minor), either by telephone or face to face, that the participant will be excluded from further participation in the study, as defined in Section 5.4. **All eligible maternal participants will proceed to complete the vaccination visit.**

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

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

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

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The following procedures will be performed:

- Obtain written informed consent, and assent if appropriate, from the maternal participant before performing any study-specific procedures. If the maternal participant is illiterate, she must thumbprint the ICD and it must be signed and dated by an impartial witness who was present throughout the entire informed consent process.

- Assign a single participant identifier using the IRT system.

- Obtain and record the participant demography (including complete date of birth [dd-Mmm-YYYY], sex, race, racial designation, and ethnicity). The date of birth will be collected to critically evaluate the immune response and safety profile by age.

- Obtain and record current/former alcohol, tobacco, marijuana, or any illicit drug usage.

- Obtain and record any medical, surgical, and obstetric history of clinical significance including history from prior and current pregnancy(ies).

- Record the LMP and estimated delivery date (EDD).

- Measure and record vital signs, including oral temperature, seated blood pressure, and heart rate.

- Record the prepregnancy BMI in the source documentation. If the prepregnancy BMI is not available, record the BMI at the time of the first obstetric visit during the current pregnancy.

- Perform targeted physical examination evaluating/noting any clinically significant abnormalities within the following body systems:

    - **Mandatory** - general appearance; heart; lungs; abdomen.

    - **Discretionary** - skin; head, eyes, ears, nose, and throat; musculoskeletal; extremities; neurological; lymph nodes.

      Note: Significant medical and surgical history and abnormal observations from the physical examination will be documented and recorded in the CRF.

- Perform obstetric examination including but not limited to fetal heart tones and fetal movement.

    - Where an obstetric ultrasound examination is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination.

    - Note: Physical or obstetric examinations performed as standard of care may be admissible if performed **within 7 days** prior to the vaccination visit.

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- Obtain details of any Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given at any time during the current pregnancy.

- Obtain details of any nonstudy vaccinations given at any time during the current pregnancy.

- Obtain details of syphilis, HIV, and HBV status.

    - Note: Only participants with a documented negative syphilis test result and negative HIV antibody and HBV surface antigen test results obtained during the current pregnancy are eligible for randomization.

    - If not performed as standard of care, assessment should be performed as part of the study, locally, and vaccination of maternal participant should be deferred until the results are available and confirmed to be negative within 28 days prior to study randomization.

- **Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.**

- Ensure that the maternal participant meets none of the temporary delay criteria as described in Section 5.2.3.

- Issue the maternal participant an e-diary and provide instructions on its completion (if applicable).

    - **Note:** *E-diary completion instructions may be provided to her parent(s)/legal guardian (if a minor).*

- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures and provide instructions on their use to the maternal participant and her parent(s)/legal guardian (if a minor).

- **On the day of and prior to vaccination,** ask the maternal participant to capture the baseline systemic event measurements in her e-diary or the site staff will capture the baseline systemic event measurements in the provisioned device (if applicable for illiterate participants).

- Prior to vaccination, collect a blood sample of approximately 15 mL for serologic assessments (prevaccination blood collection should take place on the same day or within 7 days before the vaccination visit).

- Obtain the maternal participant's randomization number and investigational product kit number using the IRT system. Refer to the IRT manual for further instructions on this process.

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- Qualified site staff member(s) will administer a single-vial dose of investigational product into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IP manual for further instruction on this procedure.

- Site staff must observe the maternal participant for any acute reactions for at least 30 minutes after investigational product administration.

- Record any acute reactions in the maternal participant's source documents, on the AE page of the CRF, and on the Vaccine SAE Reporting Form as applicable.

- Ask the maternal participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination, **OR** explain to the maternal participant that a study staff member/field worker will call or visit her every day from Day 2 to Day 7 after vaccination (where Day 1 is the day of vaccination) to collect or take her temperature and record systemic events, acute local reactions, and use of antipyretic medication in a diary (if applicable).

- Ask the maternal participant or her parent(s)/legal guardian (if a minor) to contact the site staff or investigator immediately if she experiences any of the following from Day 1 to Day 7 after vaccination to determine if an unscheduled reactogenicity visit is required as detailed in Section 8.10.5 **OR** inform the maternal participant or her parent(s)/legal guardian (if a minor) that if she experiences any of the following from Day 1 to Day 7 after vaccination or is taking antipyretic medication at Day 7, then the study staff/field worker will continue to visit until resolution. Furthermore, the maternal participant will be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns as detailed in Section 8.10.5.

    - Fever ≥39.0°C (≥102.1°F).

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

    - Severe pain at the injection site.

    - Any severe systemic event.

- Inform the maternal participants or her parent(s)/legal guardian (if a minor) that if a temperature of ≥38.0°C (≥100.4°F) is recorded during the collection of diary data, she will be required to have a rapid test for malaria as per local practice and details will be recorded in the diary (if applicable, based on local practice).

- Remind maternal participants or her parent(s)/legal guardian (if a minor) that study staff may contact them to obtain additional information on events entered into the e-diary.

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- Remind maternal participants or their parent(s)/legal guardian (if a minor) to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in Section 8.2 and Section 10.2.

- Remind the maternal participant or her parent(s)/legal guardian (if a minor) to bring the completed e-diary to the next visit *(if applicable*).

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs, and the blinded dispenser/administrator completes the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.

- Maternal participants or their parent(s)/legal guardian (if a minor) will be instructed to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.

- Request the maternal participant and her parent(s)/legal guardian (if a minor) to contact the site if she goes into labor/is admitted to the maternal unit (*The study staff/field worker will contact the maternal participant prior to the next study visit to remind her, if applicable*).

8.10.2. 1-Month Follow-up Visit (Clinic or Telephone; 28 to 42 Days After Vaccination)

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

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.2.

- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Record details of any MA-RTI, including the diagnosis.

- Record details of any nonstudy vaccinations given since the last visit.

- Complete the maternal participant's source documents.

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- Record AEs and SAEs as described in Section 8.2 and Section 10.2. Note: Active elicitation and collection of AEs and SAEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination.

- The investigator or an authorized designee completes the CRF.

- Maternal participants and their parent(s)/legal guardian (if a minor) will be instructed to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.

- Request the maternal participant and her parent(s)/legal guardian (if a minor) to contact the site if she goes into labor/is admitted to the maternal unit (*The study staff/field worker will contact the maternal participant prior to the next study visit to remind her, if applicable*).

8.10.3. Delivery (Maternity Unit)

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

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.2.

- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given since the last visit.

- If available, record the maternal participant's group B streptococcal (GBS) status and if any medication was given for intrapartum antibiotic prophylaxis (IAP). Note: Positive GBS carriage should not be reported as an adverse event in the CRF if performed in the setting of routine prenatal care.

- Record details of any nonstudy vaccinations given since the last visit.

- Collect a blood sample of approximately 15 mL for serologic assessments. Note: The maternal participant's blood sample can be taken at any time during the delivery visit, **preferably before 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.

  Note: A cord blood sample of approximately 10 mL for immunogenicity assessments must also be collected. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord and after the umbilical cord has been clamped and cut. This sample should be labeled with the **infant's participant ID number.**

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- Record pregnancy outcome information, including vital status of the infant (live, stillbirth, etc.), mode of delivery (vaginal delivery or cesarean section), and the use of any assisted devices (forceps or vacuum).

- Record details of any MA-RTI, including the diagnosis.

- Record AEs as described in Section 8.2 and Section 10.2.

- Ask the maternal participants and her parent(s)/legal guardian (if a minor) to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.

- Ask the maternal participant and her parent(s)/legal guardian (if a minor) to contact the site staff or investigator if her newborn infant meets the MA-RTI study criteria OR the study staff/field worker will contact the maternal participant/legal guardian(s) weekly to remind them to report any MA-RTI (*if applicable*).

- Complete the participant's source documents.

- The investigator or an authorized designee completes the CRF.

8.10.4. 6-Month-Postdelivery Visit (Clinic, Home, or Telephone; 180 to 210 Days After Delivery)

- Obtain details of any postnatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [eg, HBIG]) or Rho(D) immune globulin [eg, RhoGAM]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record details of any nonstudy vaccinations given since the last visit.

- Record details of any MA-RTI, including the diagnosis.

- Ask the maternal participant and her parent(s)/legal guardian (if a minor) to contact the site staff or investigator if her infant meets the MA-RTI study criteria OR the study staff/field worker will contact the maternal participant/legal guardian(s) weekly to remind them to report any MA-RTI, if applicable.

- Record AEs as described in Section 8.2 and Section 10.2.

- Complete the maternal participant's source documents.

- The investigator or an authorized designee completes the CRF.

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8.10.5. Unscheduled Reactogenicity Visits

If the maternal participant or her parent(s)/legal guardian (if a minor) reports 1 or more of the following, a contact **must** occur as soon as possible between the maternal participant and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled reactogenicity visit is required **OR** based on local practice in certain countries/locales, maternal participants will be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns regarding reactogenicity events, including:

- redness at the injection site on the arm in which the investigational product was administered measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site on the arm in which the investigational product was administered measuring >20 measuring device units (>10.0 cm),
- severe injection site pain on the arm that the investigational product was administered,
- fever ≥39.0°C (≥102.1°F).

A site visit or referral to a healthcare facility should be scheduled as soon as possible to assess the extent of the reaction, unless:

- The maternal participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The participant/study staff/field worker recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator or appropriate designee determines that the visit is not required.

This contact will be recorded in the maternal participant's source notes and in the CRF.

Any ongoing reactions must be assessed at the next scheduled visit.

The reactogenicity events should be assessed by the investigator or a medically qualified member of the site staff such as a study physician or a study nurse, as applicable to the investigator's local practice or healthcare facility, who will:

- Measure oral temperature.
- Measure the participant's heart rate.
- Measure the participant's blood pressure (seated).

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- Measure the minimum and maximum diameters of redness (if present) on the arm in which the investigational product was administered.
- Measure the minimum and maximum diameters of swelling (if present) on the arm in which the investigational product was administered.
- Assess if necrosis is present at the injection site on the arm in which the investigational product was administered.
- Assess if any exfoliative dermatitis is present.
- Assess any injection site pain on the arm in which the investigational product was administered that is present in accordance with the reactogenicity grading scale provided in Section 8.2.1.1.
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 8.2.1.2.
- Ask the participant or her parent(s)/legal guardian (if a minor) if she attended an emergency room visit or was hospitalized.
- For severe pain at the injection site resulting in an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, any necrosis on the arm in which the investigational product was administered, or exfoliative dermatitis, the investigator or qualified designee must assess these events in accordance with the intensity AE grading scale provided in Section 8.2.1.1 and Section 8.2.1.2.
- Record AEs and SAEs as described in Section 8.2 and Section 10.2.
- Complete the participant's source documents.
- The investigator or an authorized designee will complete the CRFs.
- The study staff/field worker may contact the participant to obtain additional information on events entered into the e-diary, as appropriate.

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8.10.6. RTI Surveillance Procedures and Telephone Contact Criteria – Maternal Participants

- Starting from Day 1 after vaccination (where Day 1 is the day of vaccination) until the end of the study, all maternal participants will be monitored for MA-RTIs as detailed in Section 1.2.3.1 and Section 8.1.2. Maternal participants or their parent(s)/legal guardian (if a minor) should notify the site and/field worker of the occurrence of any MA-RTIs immediately but no later than the next study visit. Note: Site contact may be by an electronic method of communication (including but not limited to electronic messaging, short message service [SMS], text, email), by phone call, or by face-to-face contact.

- The definition of maternal RTI includes 1 or more of the following signs and/or 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

- Record the details of any MA-RTI, including the diagnosis, the medically attended visit location (hospital, outpatient visit, emergency room, urgent care, or home visit), duration of hospitalization, intensive care unit (ICU) duration if applicable, prescribed medications for the MA-RTI, assessments including RSV test result (eg, NAAT, rapid antigen detection tests, or any other molecular diagnostic test), if available, and the final diagnosis.

- Record the details of any nonstudy vaccinations.

- Record AEs as described in Section 8.2 and Section 10.2. *Note: MA-RTIs are study endpoints and should not be reported as AEs.*

- Complete the participant's source documents.

- The investigator or an authorized designee completes the CRF.

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8.11. Procedures – Infant Participants

8.11.1. Infant Participants: Visit 1 – Birth (Hospital, Birth to 7 Days After Birth)

- Manually assign a single infant participant identifier. This will be assigned manually by the site using the following convention: the infant participant's identifier will be the maternal participant's IRT-generated numeric ID but with the fifth digit changed to a 2 (eg, if the maternal participant is given number 10011001, then the infant will be 10012001).

- Collect a cord blood sample of approximately 10 mL for immunogenicity assessments. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord and after the umbilical cord has been clamped and cut. This sample should be labeled with the **infant's participant ID number**.

- If cord blood is unavailable, a blood sample may be collected from the infant participant preferably within 24 hours, but up to 7 days after birth. The volume of blood collected will be based on the weight of the infant (refer to Table 3).

- Ensure and document that all the infant inclusion criteria and none of the infant exclusion criteria are met.

- Collect demography (including complete date of birth [ie, dd-Mmm-YYYY], sex, race, and ethnicity). The date of birth will be collected to critically address efficacy analyses and evaluate the immune response and safety profile by age.

    - Obtain and record the infant's length, head circumference, and weight at birth.

    - Obtain and record the infant's birth data, including GA and appearance, pulse, grimace, activity, and respiration (Apgar) score.

    - Obtain and record background factors as described in Section 10.5.

    - Measure vital signs, including temperature, heart rate, oxygen saturation by pulse oximetry, and respiratory rate.

    - Standard-of-care vital signs and examination procedures can be considered for use in the study provided they were performed within **72 hours** after birth. Note: Please reference the physical examination procedures below for details.

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

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  - Record details of any congenital anomalies on the AE page of the CRF, and report as an SAE as described in Section 10.2.3.

- Record any medication as described in Section 6.5.6.
- Obtain details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given to the infant participant since birth.
- Record AEs as described in Section 8.3 and Section 10.2.
- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.
- Review the weekly contact schedule with the parent(s)/legal guardian(s) and collect contact information **OR** remind the parent(s)/legal guardian(s) that a field worker will contact them weekly to remind them to report any MA-RTI (if applicable).
- Ask the parent(s)/legal guardian(s) to contact the investigator or qualified designee immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI visit criteria. An RTI study visit, along with a nasal swab collection, must be performed for all MA-RTIs as described in Section 1.2.4.1 and Section 8.11.7.
- **If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster),** review the nasal swab collection and shipping instructions with the infant's caregiver to ensure he/she acknowledges understanding of requirements as detailed in Section 8.11.7.1.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.11.2. Visit 2 – 1-Month Follow-up (Clinic or Home, 28 to 48 Days After Birth)

- Obtain and record background factors as described in Section 10.5.
- Obtain and record the infant's length, head circumference, and weight.
  Note: Standard-of-care measurement procedures can be considered for use at this study visit, if they were performed within the window of this study visit.
- Measure vital signs, including temperature, heart rate, oxygen saturation by pulse oximetry, and respiratory rate. Note: Standard-of-care measurement procedures can be considered for use at this study visit, if they were performed within the window of the study visit.

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- Perform a targeted physical examination, if not performed as part of standard of care, noting any clinically significant abnormalities in the site source documents. Newly identified abnormal findings must be recorded on source documents and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF. Note: Standard-of-care examination procedures can be considered for use at this study visit, if they were performed within the window of the study visit.
    - Record details of any newly emergent congenital anomalies on the AE page of the CRF, and report as an SAE as described in Section 10.2.3.
- Record details of any NDCMCs.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.2.
- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.
- Ask the parent(s)/legal guardian(s) to contact the investigator or qualified designee immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI visit criteria. An RTI study visit, along with a nasal swab collection, must be performed for all MA-RTIs as described in Section 1.2.4.1 and Section 8.11.7.
- **If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster),** review the nasal swab collection and shipping instructions with the infant's caregiver to ensure he/she acknowledges understanding of requirements as detailed in Section 8.11.7.1.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.
- Contact the infant participant's parent(s)/legal guardian(s) approximately every 7 days from birth until the 6-month follow-up visit to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the MA-RTI visit criteria. The weekly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.7.1 for guidance on reported cases of MA-RTIs in infant participants during the first 6 months after birth.

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8.11.3. Visit 3 – 6-Month Follow-up Visit (Clinic or Home, 180 to 210 Days After Birth)

- Obtain and record background factors as described in Section 10.5.

- Obtain and record the infant's length, head circumference, and weight.
  Note: Standard-of-care measurement procedures can be considered for use at this study visit, if they were performed within the window of the study visit.

- Perform a targeted physical examination, if not performed as part of standard of care, noting any clinically significant abnormalities in the source documents. Newly identified abnormal findings must be recorded on source documents and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF.
  Note: Standard-of-care examination procedures can be considered for use at this study visit, if they were performed within the window of the study visit.

  - Record details of any newly emergent congenital anomalies on the AE page of the CRF, and report as an SAE as described in Section 10.2.3.

- Record details of any NDCMCs.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record AEs as described in Section 8.3 and Section 10.2.

- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

- Contact the infant participant's parent(s)/legal guardian(s) approximately every month (28 to 35 days) until the end-of-study visit, to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the MA-RTI visit criteria. The monthly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.8 for guidance on reported cases of MA-RTIs in infant participants.

- Ask the parent(s)/legal guardian(s) to contact the investigator immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI visit criteria. **An RTI study visit, along with a nasal swab collection, must be performed for all hospitalizations due to an RTI and severe MA-LRTIs as described in Section 1.2.4.1 and Section 8.11.8.**

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- **If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster),** review the nasal swab collection and shipping instructions with the infant's caregiver to ensure he/she acknowledges understanding of requirements as detailed in Section 8.11.8.

8.11.4. Visit 4 – 12-Month Follow-up (Clinic or Telephone; 350 to 378 Days After Birth)

- Obtain and record background factors as described in Section 10.5.
- Obtain and record the infant's length, head circumference, and weight *(only applicable if a clinic visit is conducted).* Note: Standard-of-care measurement procedures can be considered for use at this study visit, if they were performed within the window of the study visit.
- Perform a targeted physical examination, if not performed as part of routine care *as described above*, noting any clinically significant abnormalities in the source documents. Newly identified abnormal findings must be recorded on source documents and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF. *Only applicable if a clinic visit is conducted.* Note: Standard-of-care examination procedures can be considered for use at this study visit, if they were performed within the window of the study visit.
- Obtain and record details of any NDCMCs or newly emergent congenital anomalies.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.2.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the end-of-study CRF for all infant participants except for infant participants born during the first year of the study.
- The investigator or an authorized designee completes the CRF for infant participants born during the first year of the study. *Note: An additional 12-month blinded follow-up period for longer-term RTI surveillance and safety oversight will be included for these participants.*
- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.
- Confirm the understanding of the infant participant's parent(s)/legal guardian(s) regarding site contact for the study, which is approximately every month (28 to 35 days) until the end-of-study visit. Ask the parent(s)/legal guardian(s) to contact the investigational site/field worker promptly if the infant meets the MA-RTI visit criteria.

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The monthly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.8 for guidance on reported cases of MA-RTIs in infant participants.

- *Infant participants born during the first year of the study only*: Ask the parent(s)/legal guardian(s) to contact the investigator immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI visit criteria.
  An RTI study visit, along with a nasal swab collection, must be performed for all hospitalizations due to an RTI and severe MA-LRTIs as described in Section 1.2.4.1 and Section 8.11.8.

- **If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster),** review the nasal swab collection and shipping instructions with the infant's caregiver to ensure he/she acknowledges understanding of requirements as detailed in Section 8.11.8.

8.11.5. Visit 5 – 18-Month Follow-up Visit (Telephone; 525 to 574 Days After Birth; Infant Participants Born During the First Year of the Study Only)

- Obtain and record background factors as described in Section 10.5.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Obtain and record details of any NDCMCs or newly emergent congenital anomalies.

- Record AEs as described in Section 8.3 and Section 10.2.

- Ensure the parent(s)/legal guardian(s) is comfortable with the chosen communication technology as described in Section 8.12.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

- Contact the infant participant's parent(s)/legal guardian(s) approximately every month (28 to 35 days) until the end-of-study visit, to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the MA-RTI visit criteria. The monthly contact may be a text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.11.8 for guidance on reported cases of MA-RTIs in infant participants.

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- Infant participants born during the first year of the study only: Ask the parent(s)/legal guardian(s) to contact the investigator immediately if any significant illness or hospitalization occurs or if the infant meets the MA-RTI visit criteria**.**
  An RTI study visit, along with a nasal swab collection, must be performed for all hospitalizations due to an RTI and severe MA-LRTIs as described in Section 1.2.4.1 and Section 8.11.8.

- **If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster)**, review the nasal swab collection and shipping instructions with the infant's caregiver to ensure he/she acknowledges understanding of requirements as detailed in Section 8.11.8.

8.11.6. Visit 6 – 24-Month Follow-up Visit (Clinic or Telephone; 714 to 742 Days After Birth; Infant Participants Born During the First Year of the Study)

- Obtain and record background factors as described in Section 10.5.

- Obtain and record the infant's length, head circumference, and weight *(only applicable if a clinic visit is conducted)*. Note: Standard-of-care measurement procedures can be considered for use at this study visit, if they were performed within the window of the study visit.

- Perform a targeted physical examination, if not performed as part of routine care, noting any clinically significant abnormalities in the source documents. Newly identified abnormal findings must be recorded on source documents and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF. *Only applicable if a clinic visit is conducted.* Note: Standard-of-care examination procedures can be considered for use at this study visit, if they were performed within the window of the study visit.

- Obtain and record details of any NDCMCs or newly emergent congenital anomalies.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record AEs as described in Section 8.3 and Section 10.2.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the end-of-study CRF for all infant participants born during the first year of the study.

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8.11.7. Active RSV Surveillance Procedures and Visit Criteria (Birth to 6 Months After Delivery)

- This is an active surveillance period spanning from birth through 6 months after delivery (Visit 3). Note: Reporting MA-RTI events should commence 72 hours after the infant's delivery. Respiratory distress events associated with and within 72 hours of birth should not be captured as MA-RTI events for the study but should be captured as AEs/SAEs (if applicable).

- The sponsor may alter the frequency of the weekly contacts or the duration of surveillance for MA-RTI based on RSV surveillance data or other operational factors.

8.11.7.1. Study Visits Following a Medically Attended RTI – Hospital, Home, or Clinic Visit

- Contact the infant participant's parent(s)/legal guardian(s) approximately every week (7 to 10 days) from birth until Visit 3 (6-month follow-up visit), to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the criteria for an MA-RTI event. The weekly contact may be via the e-diary device or study-related mobile application, text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Table 1 regarding clinical signs and symptoms that meet the study definition of an MA-RTI, and Section 1.2.4.1 for study-required assessments.

- Note: In the event that restrictions prevent taking RTI study swabs because of an outbreak, pandemic situation, or natural disaster, the study nasal swab can be collected for processing at a Pfizer central laboratory by:

  - The infant caregiver during or within 10 days following the MA-RTI visit

  OR

  - The HCP assessing the infant during the MA-RTI visit

- Note: If the parent(s)/legal guardian(s) reports to the investigational site staff that the infant has experienced an event requiring a visit to a healthcare provider, the site staff and/field worker should confirm, based on information provided, whether the event meets the criteria for an MA-RTI. Please refer to Table 1 and Section 8.1 regarding clinical signs and symptoms that meet the study definition of an MA-RTI, and Section 1.2.4.1 for study-required assessments.

- When an infant MA-RTI criterion is met or confirmed, the site/field worker will obtain records from the medically attended visit and record the healthcare information as detailed in Appendix 6.

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- When an infant MA-RTI criterion is met or confirmed, the **infant participant** will be seen as soon as possible and optimally **within 72 hours** or up to 10 days for an RTI study visit by the investigational site staff or qualified designee.

- The infant participant may be seen either at the time of the MA-RTI, at home or at the study site (if discharged), or if the infant participant has been hospitalized or is receiving treatment at another medical facility, the site staff/field worker can conduct the RTI study visit at those facilities.

    - If the RTI study visit is not performed within 72 hours of the event, it should still be performed, including the collection of nasal swab specimens.

    - Targeted assessments at an RTI study visit include but are not limited to:

        - **Respiratory signs:** lower chest wall indrawing.

        - **Vital sign assessment:** temperature, respiratory rate, heart rate, and oxygen saturation by pulse oximetry. Note: It is recommended that the participant not be receiving supplemental oxygen at the time of measurement.

        - **Nasal swab collection** from the infant participant for testing at the central laboratory.

        - Body weight

- Obtain and record background factors as described in Section 10.5.

- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.

- Record AEs as described in Section 8.3 and Section 10.2. *Note: MA-RTIs are study endpoints and should not be reported as AEs.*

- Request that the parent(s)/legal guardian(s) contact the site/field worker if the infant's illness worsens, or if the infant is hospitalized.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

- Compile the adjudication submission package for the event as detailed in Section 8.1.

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8.11.8. Long-Term RSV and Safety Surveillance Procedures and Visit Criteria

- *This is a long-term surveillance procedure for all infant participants from 6 months after delivery (Visit 3) until the last study visit.*

- Contact the infant participant's parent(s)/legal guardian(s) approximately every month (28 to 35 days) from Visit 3 (6-month follow-up visit) until the end-of-study visit, to remind the parent(s)/legal guardian(s) to contact the investigational site promptly if the infant meets the criteria for an MA-RTI visit. The monthly contact may be via the e-diary device or study-related mobile application, text, email, phone call, or face-to-face contact with the site staff/field worker. Please refer to Section 8.1 regarding clinical signs and symptoms that meet the study definition of an MA-RTI, and Section 1.2.4.1 for study-required assessments.

- Note: In the event that restrictions prevent taking RTI study swabs because of an outbreak, pandemic situation, or natural disaster, the study nasal swab can be collected for processing at a Pfizer central laboratory by:

  - The infant caregiver during or within 10 days following the MA-RTI visit

  OR

  - The HCP assessing the infant during the MA-RTI visit

- Note: If the parent(s)/legal guardian(s) reports to the investigational site staff that the infant has experienced an MA-RTI, the site should obtain additional information and determine whether the event also meets the study definition of a severe MA-LRTI.

  - Note: Severe MA-LRTI is defined in Table 1.

- The site/field worker will obtain records from the medically attended visit and record the healthcare information as detailed in Appendix 6.

- When an infant MA-RTI criterion is confirmed and also meets the study definition of hospitalization due to an RTI or a severe MA-LRTI, the **infant participant** will be seen as soon as possible and optimally **within 72 hours or up to 10 days** for an RTI study visit that includes a nasal swab collection by the investigational site staff/field worker. The staff/field worker will obtain the nasal swab optimally **within 72 hours or up to 10 days** of the event with the infant participant either at home (if discharged) or, if the infant participant has been hospitalized or receiving treatment at another medical facility, the site staff/field worker will conduct the visit at those facilities.

  - **Note:** Nasal swab collection from the infant participant is for testing at the central laboratory.

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- A targeted RTI study visit will be required for all reported cases of hospitalization due to an RTI or severe MA-LRTI only, and this includes but is not limited to:
  - **Respiratory signs**: lower chest wall indrawing, failure to respond/unconsciousness.
  - **Vital sign assessment:** temperature, respiratory rate, heart rate, and oxygen saturation by pulse oximetry. Note: It is recommended that the participant not be receiving supplemental oxygen at the time of measurement.
  - Body weight
- A targeted RTI study visit is not required for an MA-RTI event not meeting the definition of hospitalization due to an RTI or severe MA-LRTI.
- Obtain and record background factors as described in Section 10.5.
- Obtain and record details of the MA-RTI event, including emergency room or hospitalization details with admission and discharge date (if applicable).
- Record any medication as described in Section 6.5.6.
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.2. *Note: MA-RTIs are study endpoints and should not be reported as AEs.*
- Request that the parent(s)/legal guardian(s) contact the site if the infant's illness worsens, or if the infant is hospitalized.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.
- Compile the adjudication submission package for hospitalizations due to an RTI and severe MA-LRTI events only as detailed in Section 8.1.

8.12. Nasal Swab Collection

Midturbinate nasal swabs will be collected from infant participants following any MA-RTI visit during the RSV surveillance period from 72 hours after delivery until Visit 3, and for all hospitalizations due to an RTI and severe cases of an MA-LRTI during the RTI surveillance period from Visit 3 until the end of the study (see Section 1.2.4.1 and Table 1).

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The nasal swab sample is to be collected as soon as possible and optimally within 72 hours or up to 10 days of an MA-RTI visit in either the infant participant's home or a medical setting (eg, clinic, hospital, etc.) by the investigational site staff.

If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster), the nasal swab can be collected by the infant's caregiver or the HCP assessing the infant (in addition to any samples obtained in the course of routine clinical care) for processing at a Pfizer central laboratory, as detailed in Section 8.11.7.1 and Section 8.11.8.

In the event that these restrictions prevent taking RTI study swabs at the investigational site, the infant's caregiver will be given a study nasal swab collection kit including shipping instructions, to be used if necessary. The infant caregiver or the HCP assessing the infant during an MA-RTI visit may assist the investigational sites by collecting of the study nasal swab samples, as required.

Note: Investigational site staff will review the procedures for nasal swab sample collection and shipping instructions with each infant caregiver and ensure that he/she understands the appropriate procedures for collecting and packaging samples for shipment to the study site.

The process for nasal swab collection and transport to the Pfizer central laboratory via study sites is detailed in the ISF.

8.13. Communication and Use of Technology

In a study of this duration that is event-driven, it is vital to ensure that communication between the study site and the maternal participant and parent(s)/legal guardian(s) is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant (maternal and/or infant participant), to ensure that communication is maintained, and study information can be transmitted securely. Using appropriate technology, a communication pathway between the maternal participant and parent(s)/legal guardian(s) and the study site staff will be established. The maternal participant and the parent(s)/legal guardian(s) may be able to utilize their own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator.
- The ability of the maternal participant/parent(s)/legal guardian(s) to report MA-RTI visits associated with the infant participant.
- An alert in the event that the maternal or infant participant is hospitalized.
- Visit reminders.

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- Messages of thanks and encouragement from the study team.

- A platform for recording local reactions and systemic events (e-diary).

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

The null hypothesis to be tested concerns VE for the primary endpoints. The RSV vaccine will be compared to placebo, testing the hypotheses H_0: VE $\leq$20% vs H_a: VE >20%. For all secondary efficacy endpoints, the RSV vaccine 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.

9.1.1. Estimands – Infant Participants

9.1.1.1. Efficacy

In infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with key protocol criteria (evaluable participants):

- VE, defined as the percentage relative risk reduction in the incidence of MA-LRTI due to RSV in the RSV vaccine group, relative to the placebo group;

- VE, defined as the percentage relative risk reduction in the incidence of severe MA-LRTI due to RSV in the RSV vaccine group, relative to the placebo group;

- VE, defined as the percentage relative risk reduction in the incidence of hospitalization due to RSV in the RSV vaccine group, relative to the placebo group;

- VE, defined as the percentage relative risk reduction in the incidence of all-cause MA-LRTI in the RSV vaccine group, relative to the placebo group.

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

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9.1.1.2. Immunogenicity

In infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants):

- Functional antibody levels estimated by the GMT for RSV A and RSV B serum neutralizing titers.
- Geometric mean ratio (GMR), estimated by the ratio of the GMTs for RSV A and RSV B serum neutralizing titers of the RSV vaccine group to the placebo group.

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.1.3. Safety

In infant participants born to the maternal participants receiving 1 dose of investigational product:

- The percentage of infant participants with specific birth outcomes.
- The percentage of infant participants having AEs from birth through 1 month of age.
- The percentage of infant participants having SAEs, NDCMCs, and new diagnosed congenital anomalies from birth through the last study visit.

Missing AE dates and missing AE intensity will be handled according to Pfizer safety rules.

9.1.2. Estimands – Maternal Participants

9.1.2.1. Immunogenicity

In maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants):

- The immune response, estimated by the GMT for RSV A and RSV B serum neutralizing titers.
- The immune response, estimated by the GMFR from baseline in RSV A and RSV B serum neutralizing titers.
- GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum neutralizing titers of the RSV vaccine group to the placebo group.

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- Geometric mean of the IgG levels against RSV prefusion F.
- Geometric mean of the Ig levels to nonvaccine RSV antigens.

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.2.2. Safety

In maternal participants receiving 1 dose of investigational product:

- The percentage of maternal participants reporting AEs through 1 month after vaccination.
- The percentage of maternal participants reporting obstetric complications and SAEs through the end of the study.
- The percentage of maternal participants reporting local reactions within 7 days of vaccination.
- The percentage of maternal participants reporting systemic events within 7 days of vaccination.

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

9.2. Sample Size Determination

This is an event-driven study. Sample size is determined as the number of participants to be randomized that is expected to accrue the required number of endpoint cases in the evaluable population. In this study there are 2 primary endpoints, and success on either primary endpoint is sufficient (see Section 9.1); power for the study overall is therefore at least as high as the power for either primary endpoint individually. In order for the study to have at least 90% power to reject the null hypothesis for MA-LRTI due to RSV when true VE is 60%, a total of 124 cases of MA-LRTI due to RSV within 90 days of birth are required in the evaluable population. This also accounts for potential use of an alpha of 1.25% 1-sided within the multiplicity adjustment. There is no explicit case target for the endpoint of severe MA-LRTI due to RSV; depending on the assumed true VE, power for that individual hypothesis may be lower, but the power for the primary endpoint family will be at least 90%. Hypotheses about VE may be restated as hypotheses about the proportion of cases in the RSV vaccine group, conditional upon a fixed total number of cases. If this proportion is p, the null hypothesis H_0: VE $\leq$20% is equivalent to H_0: $p \geq 0.444$; the assumption of VE = 60% corresponds to $p = 0.286$. Power was evaluated by the exact binomial test, and the case target established as that number k for which power is guaranteed to be at least 90%, for all $k^* \geq k$. The calculation accounted for the study design (1:1 randomization of participants to

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RSV vaccine : placebo), planned interim analyses of efficacy (see Section 9.5), and an overall type 1 error of 2.5% 1-sided across the 2 primary endpoints.

This global study is planned to be conducted in the US and other high-income countries as well as LMICs. Incidence rates of the primary endpoints are expected to vary in different regions. Based on a recently completed Phase 3 trial of an RSV vaccine, the assumed incidence rate for MA-LRTI due to RSV through 90 days in low-incidence countries, such as the US, is approximately 1.75%; and in other regions is approximately 3.90%. With these assumptions, and also allowing for 60% VE and 10% of enrolled participants being nonevaluable, enrollment of approximately 6900 participants is planned for the study as a whole. The exact number of participants required to accrue the case target may be higher or lower than this, depending on incidence rates, observed VE, and the proportion of evaluable participants.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined for infant and maternal participants:

Population	Description
Enrolled	All maternal participants who sign the ICD.
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 eligible, are born to the maternal participants who received the investigational product to which they were randomized at least 14 days prior to delivery, did not receive palivizumab or another monoclonal antibody targeting RSV, have no major protocol violations, and did not have transfusions of more than 20 mL/kg of any blood products at <180 days.
Modified intent-to-treat (mITT) efficacy – infant	All infant participants who are born to vaccinated maternal participants.
Evaluable immunogenicity – infant	All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
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, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
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.

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Population	Description
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.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for the first planned analysis and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	• The analysis of efficacy will use 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. The incidence of MA-LRTI due to RSV and severe MA-LRTI due to RSV in infant participants will be evaluated in both groups up to 90 days, 120 days, 150 days, and 180 days after birth. • The infant evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the infant mITT efficacy population. • The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV will be tested in parallel using a multiplicity adjustment procedure. Success of the trial requires rejection of the null hypothesis (ie, a CI lower bound >20%) for either one of the 2 primary endpoints. • The primary endpoint of severe MA-LRTI due to RSV may be demoted to a secondary endpoint if there are insufficient cases for an adequately powered analysis. During the trial, blinded accrual of cases will be monitored and prior to any unblinding, a decision rule for this change will be established based on the total number of cases of severe MA-LRTI due to RSV. • Testing of the 2 primary endpoints across the time intervals will follow a fixed sequence with a gatekeeping strategy. First, the hypothesis

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Endpoint	Statistical Analysis Methods
	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 multiplicity adjustment for the 2 endpoints. If that null hypothesis cannot be rejected, testing ends. Otherwise, testing proceeds to 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. Refer to the SAP for full details of the testing sequence and multiplicity correction strategy. • There may be up to 2 interim analyses of the MA-LRTI-due-to-RSV endpoint when there is an adequate number of cases (at least 43 cases within 90 days). 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, if there are 2 interim analyses at 43 cases and 62 cases, the appropriate 1-sided significance levels are 0.00014 at the first interim analysis, 0.0015 at the second interim analysis, and 0.0245 at the final analysis. Implementation of these 1-sided significance levels ensures the overall type 1 error for the primary endpoint will be no more than 0.025. See Section 9.5 for more details. • At the interim analyses there will also be an assessment for futility, based on conditional power for the MA-LRTI-due-to-RSV endpoint. If the probability of success at the end of the trial is low, given the interim analysis results and the initially assumed VE is applied to the remaining data, consideration will be given to stopping the study for futility. • CIs for VE will be calculated using the appropriate multiplicity-adjusted alpha level α. If the lower 100(1 - α)% confidence limit for VE exceeds 20%, the null hypothesis for that endpoint will be rejected. • At the end of the trial, the RSV vaccine may be deemed efficacious if there are 42 or fewer cases of MA-LRTI due to RSV in the RSV vaccine group out of the 124 total endpoint cases. This corresponds to an estimated VE = 49%, with a 97.6% CI = (21%, 68%). For severe MA-LRTI, assuming a total of 50 cases occur, the vaccine may be deemed efficacious if there are 13 or fewer cases in the RSV vaccine group. This corresponds to an estimated VE = 65%, with a 97.6% CI = (26%, 85%). For both of these examples, it is assumed a 1-sided alpha of 0.01225 applies to the endpoint in question.

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Endpoint	Statistical Analysis Methods
	• Kaplan-Meier curves showing accrual of endpoint cases over 180 days will be presented. • There will be a sensitivity analysis of the primary endpoints to examine the impact of missing RSV swab results. Details are provided in the SAP.
Secondary	• The analysis of secondary efficacy endpoints will use the exact conditional binomial method, as for the primary endpoint. Secondary endpoints will be examined at the final analysis only. VE will be estimated along with 2-sided 95% CI. • Inference for the secondary endpoints will be conditional upon demonstrating success for one 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 1 error across primary and secondary endpoint families at no more than 2.5% 1-sided. Multiplicity correction strategies will be defined in the SAP. 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. Testing will only proceed to later time points conditional on success of all previous time points. • The infant evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the infant mITT efficacy population.
Exploratory	• The incidence in infant participants of MA-RTIs due to RSV with protocol-defined criteria occurring within 730 days after birth will be summarized. • The incidence in infant participants of MA-RTIs due to any cause with protocol-defined criteria occurring within 730 days after birth will be summarized. All MA-RTIs and severe MA-LRTIs will be summarized separately. • The incidence in infant participants of MA-LRTIs due to RSV occurring 361 to 730 days after birth will be summarized. • The incidence in infant participants of severe MA-LRTIs due to RSV occurring 181 to 730 days after birth will be summarized.

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Endpoint	Statistical Analysis Methods
	• The incidence in infant participants of hospitalization due to RSV occurring 181 to 730 days after birth will be summarized. • The primary endpoint through 180 days after birth will be summarized separately as cases associated with RSV subgroup A or RSV subgroup B infection. • The primary endpoint through 180 days after birth will be summarized by interval from vaccination to delivery and by GA at the time of vaccination. • The incidence of MA-RTI, MA-LRTI, and severe MA-LRTI due to RSV occurring 0 to 730 days after birth in premature infants (<37 weeks GA) will be summarized. • The incidence of MA-RTI due to any cause in maternal participants from vaccination through 180 days after delivery will be summarized.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	• The point estimate and exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event for each vaccine group. • A 3-tier approach will be used to summarize AEs. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in the percentage of participants reporting the events between the RSV vaccine group and the placebo group will be calculated using the test statistic proposed by Miettinen and Nurminen; in addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. A Medical Dictionary for Regulatory Activities (MedDRA) preferred term is defined as a Tier 2 event if there are 1% or more participants in at least 1 vaccine group reporting the event. • The safety analyses are based on the safety population. Participants will be summarized by the vaccine group corresponding to the vaccine they (for maternal participants) or their mothers (for infant participants) actually received. Missing e-diary data will not be imputed; missing AE

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Endpoint	Statistical Analysis Methods
	dates and missing AE intensity will be addressed using the Pfizer safety rules.
Secondary	• The point estimate and exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event for each vaccine group. • The safety analyses are based on the safety population. Participants will be summarized by the vaccine group corresponding to the vaccine they (for maternal participants) or their mothers (for infant participants) actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE intensity will be addressed using the Pfizer safety rules.
Exploratory	• Subgroup analyses of safety will be performed based on age at vaccination (<18 years, ≥18 years). These and other exploratory analyses will be described in the SAP, finalized before first database lock.

9.4.3. Other Analyses

9.4.3.1. Immunogenicity Analyses

Immunogenicity endpoints are exploratory in the study. The analyses of immunogenicity endpoints will be based on the evaluable populations. An additional analysis will be performed based on the mITT populations if there is enough difference between the mITT populations and the evaluable populations. Immunogenicity data for maternal participants and infant participants will be summarized separately, with the exception of maternal-to-infant placental transfer analysis. Participants will be summarized according to the vaccine group to which they (for maternal participants) or their mothers (for infant participants) were randomized.

The secondary and exploratory immunogenicity endpoints will be described by the following summaries and the 95% CIs:

- GMT of the RSV A and RSV B serum neutralizing titers at each available time point by vaccine group (maternal participants and infant participants, separately).
- GMT of the combined RSV A/B serum neutralizing titer, defined as the geometric mean of the RSV A and RSV B serum neutralizing titers, at each available time point by vaccine group (maternal participants and infant participants, separately).
- GMFR for RSV A and RSV B serum neutralizing titers from before vaccination to each available time point after vaccination by vaccine group (maternal participants only).

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- GMFR of the combined RSV A/B serum neutralizing titer, defined as the geometric mean of the RSV A and RSV B serum neutralizing titers, from before vaccination to each available time point after vaccination by vaccine group (maternal participants only).

- GMR 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 (maternal participants and infant participants, separately).

- GMR of the RSV vaccine group to the placebo group for the combined RSV A/B serum neutralizing titers at each available time point after vaccination (maternal participants and infant participants, separately).

- Geometric mean of the IgG levels against RSV prefusion F and Ig levels to nonvaccine RSV antigens at each available time point by vaccine group (maternal participants and infant participants, separately).

Empirical reverse cumulative distribution curves (RCDCs) for combinations of time points and vaccine groups will be presented for RSV A and RSV B serum neutralizing titers.

A sensitivity analysis will be performed to exclude immunogenicity data from mothers and their infants following onset of RSV infection between vaccination and delivery (based on evidence from the nonvaccine antigen assay).

Subgroup analyses of the secondary and exploratory immunogenicity endpoints will be performed, including an analysis based on GA at the time of vaccination, age at vaccination (<18 years, ≥18 years), time from vaccination to delivery, and by country subcategories. All subgroup analyses will be defined in the SAP.

In addition, the maternal-to-infant placental transfer ratio (infant/mother) of RSV A and RSV B serum neutralizing titers and associated 95% CI will be summarized.

9.4.3.2. Healthcare Utilization Analyses

Healthcare utilization endpoints are exploratory in the study; these analyses will be described in the SAP and finalized before first database lock. For these analyses, details of healthcare resource utilization for all infants will be assessed at each MA-RTI visit from 72 hours after the infant's delivery through the last study visit (730 days after birth). Univariate summaries of healthcare resource utilization variables will be compared between the RSVpreF and placebo groups. The summarized variables may include the following: number and type (eg, respiratory, reactive airway disease [RAD]/asthma/wheezing) of medical visits (eg, outpatient, urgent care, emergency room, hospitalization, ICU), length of hospital stay, requirement for mechanical ventilation (yes/no, total number of episodes, total number of hours/days on treatment), requirement for IV fluids, requirement for respiratory diagnostic procedures (eg, chest radiograph, supplemental oxygen, pulse oximetry), 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 use days).

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9.5. Interim Analyses

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. Because of the relatively low number of cases of severe MA-LRTI due to RSV expected, the interim analyses may not consider that endpoint. Interim analysis results may be used for internal business decisions regarding future study planning, stopping for futility, or stopping for early success.

The order of cases included in the interim analysis will be determined by the adjudication committee as those first confirmed as meeting 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 prior to taking a data snapshot will be included in an interim analysis.

The analysis of efficacy will utilize an O'Brien-Fleming alpha spending rule based on the fraction of cases of MA-LRTI due to RSV within 90 days available. 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. For example, to control the overall type 1 error for the primary endpoint at 2.5% 1-sided, a first interim analysis at 43 cases would use a 1-sided significance level of 0.014%. If a second interim analysis was 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%. The alpha levels used at interim and final analyses will depend on the exact fraction of cases available at the interim analysis.

Testing of the primary endpoints at the interim analysis will follow the sequence of interval-specific tests as described in Section 9.4.1. Secondary endpoints will not be tested at the interim analysis.

Futility will also be assessed using conditional power. Full details will be defined in the SAP. For example, if there are 62 cases available for the interim analysis, Table 7 indicates case splits for which stopping the study will be considered. The actual number of cases available may be slightly higher or lower than 62, and the decision rules amended accordingly.

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Table 7. 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.

Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's standard operating procedures (SOPs) will be documented and approved in the DMC charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

9.5.1. Data Monitoring Committee

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

The E-DMC will review safety data at defined intervals as specified in the charter. The E-DMC may conduct additional meetings to review safety data at other time points during the study, at its discretion, or at the request of the sponsor.

The E-DMC may review unblinded data during closed meeting sessions; however, the sponsor will remain blinded and will not be permitted access to the randomization assignments until the database is locked and unblinded.

After each meeting, the E-DMC will make recommendations that may include continuing the study with or without modification or pausing or stopping vaccination for safety or other reasons.

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The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the maternal participant and her parent(s)/legal guardian (if a minor) and answer all questions regarding the study.

Maternal participants must be informed that their participation is voluntary. Maternal participants and their parent(s)/legal guardian (if a minor) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant and her parent(s)/legal guardian (if a minor) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant and her parent(s)/legal guardian (if a minor) must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

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

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

A copy of the ICD(s) must be provided to the maternal participant or the parent(s)/legal guardian(s).

A study-specific assent form will be provided to maternal participants denoted to be "minor participants" as required by local regulations. It is to be understood as the "minor" maternal participants will participate in a trial after having received age-appropriate information and is sometimes also referred to as "knowing agreement." If the study includes minor participants who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

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

Participants and their parent(s)/legal guardian (if a minor) who are rescreened may be required to sign a new ICD as per IRB, local regulations, etc.

If during the study, the investigator determines that the maternal participant is for any reason no longer capable of providing informed consent, the infant's continued participation in the study requires consent to be obtained from the parent(s)/legal guardian as determined by local regulations, legal requirements, and the IRB/EC.

Note: For the infant participant, the term parent(s)/legal guardian denotes the "legally authorized representative."

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10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

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www.pfizer.com

Pfizer posts clinical study report (CSR) synopses and plain language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents Within Marketing Applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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Definition of what constitutes source data can be found in the site Source Data Agreement Plan.

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

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The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

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

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

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

For maternal immunization clinical studies conducted in pregnant women, data on the EDP including any SAEs/nonserious AEs as well as pregnancy outcomes are collected and analyzed in the clinical database. All SAEs are reported to Pfizer Safety using the Vaccine SAE Reporting Form. In case of a new pregnancy in a maternal participant before the end of the study, any exposure to the investigational product is reportable to Pfizer Safety within 24 hours of investigator awareness using the Vaccine SAE Reporting Form/EDP supplemental form.

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

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10.2.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

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Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, cesarean section, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Newly Diagnosed Chronic Medical Conditions

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 (eg, asthma).

10.2.3. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

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d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study via occupational exposure	Occupational exposure is not recorded.	Occupational exposure (regardless of whether associated with an AE) Note: Include all AEs/SAEs associated with occupational exposure.

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

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AE and SAE Recording/Reporting

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

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Assessment of Causality

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any anonymized postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

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Follow-up of AEs and SAEs
• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.5. Reporting of SAEs

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

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

Potential Cases of Drug-Induced Liver Injury

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below

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are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute

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hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

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

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

10.4. Appendix 4: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.4.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

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10.4.2. Definition of Serious Adverse Event, Serious Adverse Device Effect, and Unanticipated Serious Adverse Device Effect

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

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.
Unanticipated Serious Adverse Device Effect (USADE) Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.4.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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10.4.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP manual.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as "severe" should not be confused with an SAE. "Severe" is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as "severe."
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as "severe."

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Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/ device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.

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Follow-up of AE/SAE/Device Deficiency
• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.4.5. Reporting of SAEs

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

10.4.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

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10.5. Appendix 5: Background Factors

1. **Information on the following will be collected at Visit 1, Visit 4 (12-Month), and Visit 6 (24-Month) for all infant participants:**

    - Educational level of parent(s) or legal guardian(s).
    - Exposure to smoke (including tobacco smoke).
    - Number of persons in the household ≥18 years of age.
    - Number of children <18 years of age in the household and if they attend school/ daycare.
        - Number of children in the household under 5 years of age (under 60 months).
        - Number of children in the household ≥5 years of age (≥60 months).

2. **Information on the following will be collected at each postbirth visit:**

    - Childcare/daycare (for infant participants).
    - Breastfeeding information (including whether or not breastfeeding is exclusive).

3. **Information on the following will be collected at each RTI study visit:**

    - Number of missed days of work for parent(s) or legal guardian(s) due to the infant participant's illness.

10.6. Appendix 6: Healthcare Provider Assessment and Treatment Criteria Checklist for MA-RTI Visit – Infant Participants

When an infant MA-RTI medical visit criterion is met or confirmed, the site will obtain records from the medical visit and capture the healthcare information as detailed below in the eCRF. This information is based on respiratory-related assessments including examination findings, clinical findings, and any pathogen-related assessments/findings.

Medical Visit - Visit Details and Assessment Requirements

Note: This should not be linked to a study visit but may overlap with the RTI study visit. The following fields and clinical assessment details should be obtained from relevant records for the medically attended event prior to each RTI study visit to support the assessment of the RTI event.

- **Reason for visit including date/time, eg,**
    - Nasal discharge for 24 hours or more.

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- Difficulty breathing, labored breathing, or rapid breathing for any duration.
- Cough.
- Inability to feed for any duration due to respiratory symptoms.
- Apnea.
- Any other respiratory symptom of concern.

- Location of medical visit (inpatient clinic, outpatient clinic, emergency department, urgent care, hospitalization, home visit, other). ***Note: study visits should NOT be recorded here.***
  - **If hospital visit,** was this triggered by an RTI (include details pertaining to duration as well as admission and discharge information and records)?
- Clinical findings pertaining to respiratory symptoms and/or RTI, as detailed below but not limited to:
  - Presence or absence of pertinent examination findings, eg, apnea (documented as per chart), wheezing, fever, cough, nasal congestion, intercostal retractions, lower chest wall indrawing, grunting, crackles, decreased breath sounds, other abnormal breath sounds, dry mucous membranes, skin tenting, sunken fontanelle, difficulty feeding, failure to respond/unconsciousness, etc.
  - Respiratory rate from highest/worst value of visit.
  - Oxygen saturation (SpO_2) from lowest/worst value of visit.
  - Oxygen supplementation (assisted ventilation, including type of respiratory assistance [respirator, "state-of-the-art" occlusive nasal prongs, face tent, etc.]).
    - Days of supplementary oxygen.
    - Use of nasal cannula.
    - Use of high-flow nasal cannula or mechanical ventilation (ie, invasive or noninvasive).
  - Heart rate from worst value of visit when performed consistently.
  - Body weight from the date of the MA-RTI event.
  - Temperature from worst value of visit when performed consistently.
  - Additional clinical or respiratory related assessments including chest x-ray.

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- Local test results for RSV as part of routine clinical care:
    - Testing platform used (clinical list of all platforms and validated by research).
    - Result (list: positive, negative, indeterminate, other).
- Results for any local non-RSV respiratory pathogen testing conducted as part of routine clinical care:
    - Result (list: detected, not detected, indeterminate)
- Record the provider diagnosis, including any causative pathogen (if applicable), eg, RSV bronchiolitis, asthma, influenza, etc.
- Obtain details of all prescribed medications including IV fluid usage.
- Obtain details of all AEs/SAEs in line with study requirements. Note: MA-RTIs are not AEs/SAEs, unless related to the investigational product or resulting in death.

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10.7. Appendix 7: Country-Specific Appendix – Applicable to Japan Only

The following supplementary text should be read in conjunction with the C3671008 protocol:

10.7.1. Informed Consent for the Maternal Participants <20 Years Old

Informed consent for maternal participants <20 years old and their infant participants will be obtained based on current Japanese civil code article 753 until 01 April 2022.

- Married maternal participants 16 to <20 years of age are deemed to have reached "majority" and each maternal participant will sign the ICD for her and her infant's study participation.

- The maternal participants <16 years of age and unmarried maternal participants 16 to <20 years of age are deemed "minors."

    - When the maternal participant is a minor under local law, the investigator, or a person designated by the investigator, will obtain written informed consent from the maternal participant's legally acceptable representative, parent(s), or legal guardian as well as the maternal participant's assent (affirmative agreement) for her and her child's study participation before any study-specific activity is performed. The investigator will retain the original of each signed consent and assent document.

        - The assent form for a minor must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

        - The assent form for a minor used during the informed consent process must be reviewed by the sponsor, approved by the IRB before use, and available for inspection.

        - The investigator must ensure that the maternal participant's legally acceptable representative, parent(s), or legal guardian is fully informed about the nature and objectives of the study and possible risks associated with participation.

        - The source documents must record that the maternal participant was a minor at the time of signing the ICD, how the investigator determined that the person signing the consent was the maternal participant's legally acceptable representative, the consent signer's relationship to the maternal participant (eg, parent), and that the maternal participant's assent was obtained.

    - When the minor maternal participants reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study.

- Beginning on 01 April 2022, when the amended civil law in which individuals 18 years of age and older are deemed to have reached majority and marriage age for women is implemented:

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- The investigator, or a person designated by the investigator, will obtain written informed consent from the maternal participant 18 to <20 years of age and married maternal participants 16 to <18 years of age.

- For all maternal participants <16 years of age and unmarried maternal participants 16 to <18 years of age, the investigator, or a person designated by the investigator, will obtain written informed consent from the maternal participant's legally acceptable representative, parent(s), or legal guardian as well as the maternal participant's assent.

10.7.2. Temperature Measurement and Definition of Fever

- Axillary temperature will be measured at Visit 1 and as required at an unscheduled visit and will be measured by the maternal participants for 7 days following vaccination.

- For the maternal participants enrolled in Japan, an axillary temperature of ≥37.5°C (99.5°F) meets the definition of a current febrile illness in the criteria for temporarily delaying vaccine administration described in Section 5.2.3.

- For the purpose of recording the temperature in the e-diary, fever is defined as an axillary temperature of ≥38.0°C (100.4°F) for maternal participants enrolled in Japan.

10.7.3. Safety Monitoring in the Sentinel Cohort - Maternal Participants

As Study C3671008 is a first-in-Japanese study and in accordance with a recommendation from the Pharmaceuticals and Medical Devices Agency (PMDA), the study will utilize a sentinel cohort for the maternal participants enrolled in Japan with progression to study enrollment at all study sites after a safety review (data from each maternal participant through 14 days after vaccination). In addition to the study procedures and requirements specified in the protocol for Study C3671008, the following procedures will be required for the maternal participants enrolled in the sentinel cohort in Japan.

10.7.3.1. Enrollment of Maternal Participants in the Sentinel Cohort

In the sentinel cohort, approximately 8 maternal participants will be enrolled. No more than 4 maternal participants per day can be randomized. Vaccination of the remaining maternal participants in the sentinel cohort will commence no sooner than 48 hours after the fourth participant received her vaccination.

10.7.3.2. Conclusion of the Sentinel Cohort

After enrollment in the sentinel cohort is completed, the Pfizer internal review committee (IRC) will review at least 14 days of postvaccination safety data from all maternal participants enrolled in the sentinel cohort, including all local reactions, systemic events, and AEs. An acceptable review will trigger an expansion of study enrollment to all study sites in Japan. Refer to the IRC charter for further details.

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10.7.3.3. Additional Visit - Day 15 Follow-up Visit (Clinic or Telephone; 14 to 16 Days After Vaccination)

All maternal and infant participants enrolled in this study will follow the protocol for Study C3671008. In addition, the maternal participants enrolled in the sentinel cohort in Japan will have a Day 15 follow-up visit conducted either at the study site or via telephone. This visit should be conducted 14 to 16 days after vaccination.

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.2.
- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given since the last visit.
- Review the participant's e-diary data.
- Record details of any MA-RTI, including the diagnosis.
- Record details of any nonstudy vaccinations given since the last visit.
- Complete the maternal participant's source documents.
- Record AEs and SAEs as described in Section 8.2 and Section 10.2.
- The investigator or an authorized designee completes the CRF.
- Maternal participants will be instructed to contact the site to report any significant illness (new or worsening), any medically attended respiratory events (eg, doctor's visit, emergency room visit), or any hospitalization that occurs during the study period as detailed in Section 8.10.6.
- Request the maternal participant to contact the site if she goes into labor/is admitted to the maternal unit.

10.7.3.4. Schedule of Activities for Maternal Participants Enrolled in the Sentinel Cohort in Japan

The following table provides an overview of the protocol visits and procedures for the maternal participants enrolled in the sentinel cohort in Japan. Refer to Section 1.2.3.1 for the Schedule of Activities for the Maternal Participants: RTI Surveillance for Medically Attended Respiratory Tract Illness Visits (Vaccination Until the End-of-Study Visit).

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Visit Description	Screening and Vaccination[a]	Day 15 Follow-up	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	**28 Days Prior to Vaccination to Day 1**	**14 to 16 Days After Vaccination**	**28 to 42 Days After Vaccination**		**180 to 210 Days After Delivery**
Type of Visit	**Clinic**	**Clinic or Telephone**	**Clinic or Telephone**	**Maternity Unit**	**Clinic, Home, or Telephone**
Informed consent for maternal participant and her infant	X				
Assign single maternal participant identifier	X				
Demography	X				
Medical history including obstetric history[d]	X				
Record current/former alcohol, tobacco, marijuana, or any illicit drug usage	X				
Record vital signs	X				
Targeted physical and obstetric examination performed on the same day or within 7 days before the vaccination visit	X				
Record details of any antenatal and/or postnatal steroid treatment, monoclonal antibodies, blood products, or Rho(D) immune globulin	X	X	X	X	X
Record details of the maternal participant's GBS status and if any medication was given for IAP				X	
Record nonstudy vaccine information	X	X	X	X	X
Review eligibility criteria	X	X	X	X	
Review temporary delay criteria	X				
Prevaccination blood draw for serologic assessment (~15 mL) on the same day or within 7 days before the vaccination visit	X[e]				
Assign randomization and container number	X				
E-diary training, dispense digital thermometer and measuring device[f]	X				
Obtain and record baseline assessment of prespecified systemic events **on the day of and prior to vaccination** in the e-diary	X				
Administer investigational product	X				
Postvaccination observation (at least 30 minutes) and assessment of immediate AEs	X				
Delivery blood draw for serologic assessment (~15 mL)				X[e]	

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Visit Description	Screening and Vaccination[a]	Day 15 Follow-up	1-Month Follow-up[b]	Delivery[c]	6-Month Postdelivery
Visit Window (Days)	**28 Days Prior to Vaccination to Day 1**	**14 to 16 Days After Vaccination**	**28 to 42 Days After Vaccination**		**180 to 210 Days After Delivery**
Type of Visit	**Clinic**	**Clinic or Telephone**	**Clinic or Telephone**	**Maternity Unit**	**Clinic, Home, or Telephone**
Record pregnancy outcome information				X	
Review e-diary data[g]	X	X			
Record AEs, as appropriate[h]	X----------X				
Record SAEs, as appropriate[h]	X	X	X	X	X
Record details pertaining to MA-RTI visit[i]	Assessment of confirmed MA-RTI events during the study as detailed in Section 1.2.3.1 of the schedule of activities				

Abbreviations: CRF = case report form; e-diary = electronic diary; GBS = group B streptococcal; IAP = intrapartum antibiotic prophylaxis; ICD = informed consent document; MA-RTI = medically attended respiratory tract illness.

a. In countries/locales where certain prenatal assessments are not routinely performed, prerandomization assessments and test results to confirm maternal participant eligibility for this clinical trial can be obtained reviewed by the investigator or qualified designee up to 28 days prior to vaccination.
b. The 1-month follow-up visit will not be performed if delivery occurs before this visit. Active elicitation and collection of AEs and SAEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination. Once delivery occurs, the visit windows are calculated based on the delivery date.
c. The delivery visit includes the time from when a participant is admitted into labor through discharge following delivery of her infant. Please see Section 8.10.3 for required protocol assessments at this visit.
d. Where an obstetric ultrasound examination is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination. As part of the obstetric history, details regarding the last menstrual period (LMP) and estimated delivery date (EDD) are to be recorded.
e. AEs occurring up to 48 hours after a blood draw that are related to the study procedures must be reported in the CRF.
f. Maternal participants will be issued a measuring device to measure local reactions and a digital thermometer for recording daily temperatures and will be provided with instructions on their use. Maternal participants and/or the study staff/field worker (as per local practice) will record (in an e-diary) a baseline assessment of prespecified systemic events on the day of and prior to vaccination and reactogenicity events from Day 1 to Day 7 following vaccination (where Day 1 is the day of vaccination). Remind maternal participants that the study staff/field worker may contact them to obtain additional information on events entered into the e-diary. Ask maternal participants to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination, to determine if an unscheduled reactogenicity visit is required. Based on local rules of practice, the maternal participant may be referred to the appropriate healthcare facility at the discretion of the study staff/field worker if there are any concerns.
g. Site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate maternal participant compliance and as part of the ongoing safety review.
h. The investigator and site staff/field worker will ensure the active elicitation and collection of AEs through 28 days after vaccination. From the signing of the ICD until the maternal participant completes the study, all SAEs will be collected. Please see Section 8.3.1 for reporting requirements and timelines.
i. A confirmed MA-RTI is defined as an expected RTI event based on the assessments detailed in the schedule of assessments in Section 1.2.3.1. These events will not be captured as safety events, unless the investigator or an appropriate designee deems them to be related to the investigational product or to have resulted in death.

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10.7.4. Exclusion Criterion 12 Clarification

For exclusion criterion 12, "Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales." In Section 5.2.1, any current use of an illicit drug including marijuana will not be permitted for maternal participants enrolling from study sites in Japan.

10.7.5. Definitions of SAE, SAE Caused by Medical Device, and Unanticipated SAE Caused by Medical Device

Definition of SAE caused by medical device:

An SAE caused by medical device is defined as an AE caused by a medical device which led to an outcome characteristic to SAEs, or a device-related incident whose recurrence might lead to death or serious deterioration in health.

NOTE: See the Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting section (Appendix 4). Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 2 of the protocol.

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10.8. Appendix 8: Country-Specific Gestational Age Assessment Appendix – Applicable to the Philippines, Gambia, and South Africa Only

The following supplementary text should be read in conjunction with the C3671008 protocol:

Participants who have not had ultrasound assessments to determine eligibility during routine care should be consented and have an ultrasound within 90 days prior to vaccination in order to comply with inclusion criteria #1 in Section 5.1.1.

Safety endpoints:

The time period and frequency for collecting AE and SAE information by the investigator and site staff should follow Appendix 2, with the exception of the additional screening window for sites conducting ultrasounds procedures from -90 to -28 days. At these sites, the safety reporting periods should be as follows:

- AEs occurring up to 48 hours after ultrasound assessment that the investigator deems are related to the study procedure must be reported in the CRF.
- The active collection period for SAEs begins once informed consent has been provided until the maternal participant completes the study.
- The active collection period for nonserious AEs begins 28 days prior to vaccination and continues through a minimum of 28 calendar days after vaccination as described in Section 8.3.1 and Section 10.2.

MA-RTI endpoints:

Maternal MA-RTIs are collected from the time of vaccination to the end of the study period as described in Section 8.1.2.

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

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10.9. Appendix 9: Country-Specific Age Requirements Appendix - Applicable to South Korea and Taiwan Only

The following supplementary text should be read in conjunction with the C3671008 protocol:

Section 5.1.1: Inclusion criterion 1 states that healthy women ≤49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications are eligible for the study.

Please find below country-specific minimum age requirements for study entry into the protocol:

- In **South Korea**, the minimum age requirement of maternal participants who can be enrolled into the study is ≥19 years of age.
- In **Taiwan**, the minimum age requirement of maternal participants who can be enrolled into the study is ≥20 years of age.

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10.10. Appendix 10: Country-Specific Appendix – Applicable to South Korea Only

The following supplementary text should be read in conjunction with the C3671008 protocol:

Exclusion Criterion 12 Clarification

For exclusion criterion 12, "Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales." In Section 5.2.1, any current use of an illicit drug, including marijuana, will not be permitted for maternal participants enrolling from study sites in South Korea.

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10.11. Appendix 11: Country-Specific Appendix – Applicable to the Philippines Only

The following supplementary text should be read in conjunction with the C3671008 protocol Section 10.1, Appendix 1 requirements, which details the Regulatory, Ethical, and Study Oversight Considerations, including the compensation/reimbursement requirements for study participants.

Study participants enrolled in the Philippines may be compensated to cover expenses related to completion of maternal and infant study visits in accordance with country-specific applicable laws and regulations, as approved by the IRB/EC. In addition, compensation may be provided upon e-diary completion with the approval of the IRB/EC.

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10.12. Appendix 12: Country-Specific Appendix – Applicable to New Zealand Only

The following supplementary text should be read in conjunction with the C3671008 protocol:

Currently, the protocol states that a full date of birth will be collected, for both maternal and infant participants in the study as per Section 8.10.1, bullet 3, and Section 8.11.1, bullet 5, respectively. To address the HDEC's recommendation pertaining to the collection and overseas transfer of identifiable participant data, specifically the date of birth, to the Sponsor, the following modifications have been made to the respective bullets concerning the date of birth collection in the study in accordance with country-specific applicable laws and regulations:

Revised text for Section 8.10.1, bullet 3 (Maternal Participants) Obtain and record the participant demography (including ***the true year of*** **birth** ***only*** **[*01-JAN*-YYYY],** sex, race, racial designation, and ethnicity). The ***year*** of birth will be collected to critically evaluate the immune response and safety profile by age
Revised text for Section 8.11.1, bullet 5 (Infant Participants) ***Obtain and record the participant*** demography (including the complete date of birth [dd-Mmm-YYYY], sex, race, ***racial designation***, and ethnicity). The date of birth will be collected to critically ***address efficacy analyses and*** evaluate the immune response ***and safety profile by age***.

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10.13. Appendix 13: Protocol Document History

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

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	05 December 2019	N/A
Protocol amendment 1	24 March 2020	PROTOCOL SUMMARY: Clarification text was added in various sections of the main body of the protocol to match the revisions made to the protocol summary. Throughout: The protocol now contains final wording regarding the double-blinded, placebo-controlled study design and the final dose and formulation of RSVpreF. This is as a result of the analysis of the safety, tolerability, and immunogenicity data from the C3671003 maternal Phase 2b trial. Section 1.2.1 Study Design – Maternal Participants: The final dose and formulation of RSVpreF were inserted, including the lyophile match for the placebo. Section 1.2.2 Study Design – Infant Participants: The text box pertaining to the vaccine group arms was deleted. The maternal-infant dyads will be randomly assigned in this study. Rationale: Infant participants will not be administered the investigational product. Therefore, the current placement is potentially confusing to readers. Section 1.2.3 Schedule of Activities for Maternal Participants, Section 5.2.3, and Section 8.10.1: Clarification text was added as follows: o The immunogenicity blood collection and physical examination window requirements before vaccination were aligned to provide greater logistical convenience for the

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		investigational sites with respect to enrolling participants into the study. o The wording for the study objectives pertaining to the request for IAP details for maternal participants with a GBS status was revised to be consistent with the study procedural objectives, which are to collect GBS status and to ascertain whether any medication was given for IAP. This resulted in the deletion of the text in Section 6.5.3, as this information is captured in Section 8.10.3. o A reference to the immunogenicity blood draws for maternal participants was added to clarify the AE reporting requirements for events that might occur as a result of study-related procedures. Section 1.2.3.1 Schedule of Activities for Maternal Participants – Respiratory Tract Illness (RTI) Surveillance for Medically Attended Respiratory Tract Illness (MA-RTI) Visits: o Details to be collected during an MA-RTI were revised. o Clarification was added regarding the safety reporting requirements for MA-RTI events that might occur during the study. Section 1.2.4 Schedule of Activities for Infant Participants: o Visit flexibility was increased to prioritize participant safety and adherence to local guidance in the event of a COVID-19 outbreak or other outbreaks. o The physical examination and vital sign assessment windows for the study were aligned to provide greater logistical convenience for the investigational sites with respect to compliance to study protocol requirements.

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		o The protocol safety reporting criteria and period for AEs, SAEs, and NDCMCs were streamlined. Section 1.2.4.1 Schedule of Activities for Infant Participants: RTI Study Visits During the Study: The table was revised, including splitting the schedules of activities for unscheduled RTI visits for all infant participants into RTI surveillance from birth to 6 months and RTI surveillance from 6 months to the end of the study. The procedures were streamlined for these RTI study visits to improve clarity and consistency. Table 1: Clarification has been added as to when a study visit is triggered for reported MA-RTI endpoint events on the study. Day 1 is the day of the MA-RTI visit as detailed in Section 8.11.7. In addition, clarification has been added as to what constitutes the site source for confirmed study endpoint criteria, in order to provide the sites guidance on what documentation will eventually be submitted to the EAC for evaluation. Section 3.1: The exploratory endpoints were revised to correspond with the planned statistical analyses of RTI events in the pediatric population. This does not represent a change to the study design but instead better reflects the total statistical analysis plan. Section 3.1, Section 3.2, and throughout: To improve clarity and ensure consistency, the use of "RSV-neutralizing antibody titers" has been changed to RSV serum neutralizing titers." This is the sponsor's preference based on what the neutralizing activity assay is based upon, and in this case, it is whole serum and not just the purified antibodies during these immunogenicity assessments. Section 3.3, Section 8.1.1.2, Section 8.1.3, and Section 10.2: For further clarification, the protocol's safety and endpoint reporting requirements were amended to ensure consistency with Pfizer's updated

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		safety reporting requirements for endpoint-defined studies. Section 4.3: The text "availability of these data are expected in 2020" was removed as this statement does not accurately reflect the current decision-making process for the dose and formulation selection activities for this study. Section 5.2.1: Clarification text was added to the exclusion criterion for BMI and congenital anomalies based on study requirements. Section 5.2.3, Section 6.5.1, and Section 6.5.2: The Tdap administration requirements text was modified to describe the timing of vaccinations based on data from the C3671004 study, once available. This change will better reflect clinical practice and will facilitate recruitment of suitable maternal participants for the study. Section 6.1.1, Section 6.1.3, Section 8.4, and Section 8.10.1: Clarification text was added to address investigational product reconstitution volume and administration requirements. This change is to ensure consistency with the investigational product administration documentation for the study. Section 7.2: Clarification text was added to address the notification process for biological sample management in the event of study participant withdrawal from the study. Section 7.3 and Appendix 1 Informed Consent Process: Clarification text was added to address study retention and data collection requirements for the study. In addition, further clarification has been added to emphasize the informed consent process during circumstances where the maternal participant is no longer able to provide consent but the infant participant's continued participation in the study could be retained by the parent(s)/legal guardian as

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		per local regulatory, local laws, and local governance approval. Section 8.1.1.1: Clarification text was added to provide guidance regarding the midturbinate swab processing requirements and the definition of acceptable certified/accredited laboratory bodies for this process in the study. Section 8.2.1.1 and Section 8.10.1: The reporting requirements for Grade 4 local reactions in the study were clarified; the assessment and reporting are carried out by the investigators (or appropriately qualified designees). Section 8.3.1.1, Section 8.3.1.2, Section 8.3.5.1, Section 8.3.5.2, Section 8.10, and Section 8.11: The reporting requirements were clarified for this vulnerable patient population with regard to AEs and SAEs likely to occur in the study in women with GA eligibility criterion between 24 0/7 and 36 0/7 weeks. Section 8.3.6: Text was added to address and standardize reporting procedures for AESIs for this patient population. Section 8.3.7 and Appendix 4: Several Pfizer text revisions were incorporated regarding device deficiencies and the safety reporting requirements for this study. Section 8.10: The immunogenicity blood collection and physical examination window requirements before vaccination were aligned to provide greater logistical convenience for the investigational sites with respect to enrolling participants into the study. Section 8.10.1: The prepregnancy BMI text revisions in Section 5.2.1 were aligned with the study assessment requirements for maternal participants at screening.

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		Section 8.10.2, Section 8.10.3, Section 8.10.4, and Section 8.10.6: Clarification text was added to the MA-RTI reporting requirements for maternal participants in the study to provide guidance and ensure the investigational sites provide accurate information pertaining to these self-reported events. Section 8.11.1 to Section 8.11.6: Clarification text was added (where applicable) to address the following study assessments: o "Birth weight must be the first birth weight and cannot be based on the standard-of-care examination" was removed as this statement is confusing to the investigational sites. Birth weight assessments have now been realigned with standard-of-care assessments at the study visit to aid compliance with study assessments and requirements. o Clarification text was added regarding the reporting of standard-of-care measurements for vital sign assessments. o In addition, the physical examination and vital sign assessment windows for the study were aligned to provide greater logistical convenience for the investigational sites to comply with study protocol requirements. o For further clarification, the RTI study visit assessment requirements were amended to emphasize the difference between the MA-RTI visit criteria and the subsequent study visit after the event has been reported. This is to improve clarity and consistency with the RTI study visit requirements. Section 8.11.7.1: For further clarification, the RTI study visit assessment requirements have been amended to emphasize the following:

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		o The RTI study visit window, including nasal swab collection from the MA-RTI notification for the infant participant. o Duplicate text was removed pertaining to the MA-RTI definition and the signs and symptoms of interest pertinent to an RTI study visit. o Guidance regarding the difference between the MA-RTI visit and the subsequent study visit after the event has been reported. This is to improve clarity and consistency with the RTI study visit requirements. Section 8.11.8: Clarification text was added to address the RTI study visit window, including nasal swab collection from the MA-RTI notification for the infant participant. o For further clarification, the RTI study visit assessment requirements have been amended to emphasize the difference between the MA-RTI visit and the subsequent study visit after the event has been reported. This is to improve clarity and consistency with the RTI study visit requirements and provide guidance to the investigational sites. Section 9.1.2.1, Section 9.1.2.2, Section 9.4.1, Section 9.2, and Section 9.5: Text was added to clarify the statistical analysis procedures in line with the current revisions. Appendix 2: Clarification text was added to support the safety and pregnancy outcome reporting requirements for participants who may experience exposure during pregnancy while in the study. Appendix 5: Further clarification was added to the background factors of interest during the infant's participation in the study. Appendix 6: Clarification text was added to the examination and treatment criteria checklist for

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		reported MA-RTI visits. This is to ensure there is some consistency to the source records provided for these events in relation to the protocol requirements. Throughout: Several changes were made to incorporate the replacement of the Clinical Trial Serious Adverse Event Report Form (CT SAE Report Form) to Vaccine SAE Reporting Form, as part of the new vaccine SAE reporting requirements for Pfizer. Throughout: Minor editorial revisions were incorporated as appropriate.
Protocol amendment 2	26 June 2020	Section 5.1.1: Administrative update was incorporated to address the recently added Appendices 7 and 8. Appendix 7: A country-specific appendix was added for Japan to address consent/assent issues for minors, temperature measurement, definition of fever, and enrollment of maternal participants in the sentinel cohort for safety monitoring. Appendix 8: A country-specific appendix was added for the Gambia and South Africa to address an extension to the screening period for maternal participants with regard to GA requirements and consent process.
Protocol amendment 3	26 August 2020	PROTOCOL SUMMARY: Added clarification text to the exploratory endpoint section for the infant participants; changes were made in the protocol summary to match the revisions made in the main body of the protocol. Section 1.2.2: Study Design – Infant Participants: Added text to address RSV seasonality and the required RTI surveillance periods during the study. Rationale: The previous placement was potentially confusing to readers. The revisions provide clarity to

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		the investigational sites with regard to the RTI surveillance follow-up activities. Section 1.2.3 and Section 1.2.3.1: Added clarification text (where applicable) to address the following: o Added "Home or Telephone" to the type of visit options allowed for the 6-month-postdelivery visit. o Added clarification text to the alcohol history reporting requirements and included "obstetric" in the screening assessment requirements for the study. o Added "study staff," as study personnel are allowed to collect and report baseline and reactogenicity assessments reported during the evaluation period. o Added clarification text regarding the reporting requirements for AEs, SAEs, and MA-RTIs for maternal participants. Section 1.2.4 - Schedule of Activities for Infant Participants: o Added "Home" to the type of visit options allowed for the 1-month and 6-month follow-up visits and added further clarification to the visit status during potential COVID-19 pandemic situations or other natural disasters. Rationale: Infant participant visit options were aligned with the maternal participant requirements to allow for visit flexibility.

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		o For further clarification, the physical examination and vital sign assessment expectations at birth and at the 1-month visit were aligned to provide greater logistical convenience for the investigational sites to comply with study protocol requirements. Sections 1.2.4, 1.2.4.1, 8.1.1, and 8.11 to 8.12: Added clarification text (where applicable). o To address alternate nasal swab collection procedures, if needed, during potential COVID-19 pandemic situations or other natural disasters. o Clarification text was added with regards to the start of the reporting period for MA-RTI events upon the infant's delivery. This is to improve clarity and consistency with the capturing and reporting requirements for MA-RTI events and provide guidance to the investigational sites. Sections 1.2.4.1, 8.11.7.1, 8.11.8, and Appendix 6: o Added temperature and body weight measurements for infant participants during study RTI visits. o For vital sign measurements, especially oxygen saturation measurements (where applicable), clarification text was added to state that it is recommended that the participant not be receiving supplemental oxygen at the time of measurement. These updates are to ensure consistency with the study RTI assessment visits after a confirmed MA-RTI event. Section 3.1: Added clarification text as follows: o Table 1. Primary and Secondary Endpoint Events and Definitions in Infant Participants: For further clarification, added descriptive text to the table header to address endpoint events listed within the table. In addition, made corrections to the overlapping respiratory rate measurements

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		provided for some study endpoint events. These changes were made to improve clarity and consistency with the endpoint reporting and evaluation process for the study. o For the infant participant exploratory objectives, added the planned statistical analysis period of "after 6 months of age" to "all-cause MA-RTIs and hospitalizations due to RSV" in the pediatric population based on regulatory authority feedback from South Korea. o Incorporated revisions to align endpoints with study duration, specifically MA-LRTIs due to RSV A and RSV B, and MA-RTIs associated with non-RSV respiratory pathogens. o Added clarification text to address the analysis plans for the healthcare utilization endpoints. Section 4.1: For further clarification, added text to address the desire to enroll across gestational age. Section 4.3: Added a brief summary of the safety and immunogenicity results from the C3671003 trial to support the decision-making process for this study. Section 5.1.1: Inserted administrative update/clarification text with regards to: o Participant eligibility guidance documentation available within the investigator site file. o The informed consent process for maternal participants. Section 5.2.1: Based on study requirements: • Added clarification text to exclusion criterion 7, which addresses the investigator's judgment when assessing participant eligibility (maternal participant or her fetus) and regional endemic conditions during routine maternal care, as per

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		local standards of care and obstetric recommendations. • Added clarification text to address illicit drug use pertaining to marijuana. Section 5.2.2: Deleted the infant participants exclusionary criterion pertaining to the "receipt of investigational or approved monoclonal antibodies against RSV." This was to provide additional clarification to the investigational sites with regards to the infant's eligibility criteria. Sections 5.2.3, 6.5.1, and 6.5.2: Modified the Tdap administration requirements text to describe the timing of vaccinations based on recent data from the C3671004 study (A Phase 2b, Placebo-Controlled, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus [RSV] Vaccine When Administered Concomitantly With Tetanus, Diphtheria, and Acellular Pertussis Vaccine [Tdap] in Healthy Nonpregnant Women 18 Through 49 Years of Age; ClinicalTrials.gov ID: NCT04071158). Section 6.1.4: Added text to clarify what constitutes a medical device with regards to the investigational product in this study. Section 6.5.2: Added text to clarify the tetanus and diphtheria vaccine administration requirements during the study. Section 6.5.4: For further clarification, added text to address prohibited vaccinations and treatments for infant participants. This is to provide guidance to the investigational sites. Section 6.5.5: Added text to clarify the permitted treatments, vaccines, and procedures acceptable to infant participants enrolled in the study.

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		Sections 8.2.1 to 8.2.1.2 and Section 8.10.1: For further clarification, amended the e-diary completion requirements to emphasize the different reporting and/recording options for reactogenicity events should illiterate maternal participants be enrolled in the study. This is to improve clarity and consistency with the reactogenicity reporting requirements at the investigational sites. Table 6 and Section 8.2.1.3: Based on regulatory feedback, provided a description of the intensity scale for the reactogenicity event "fever." Sections 8.3.1 to 8.3.1.2, Sections 8.3.5.2 to 8.3.8.1, and Section 10.2.3: Added clarification text (where applicable) to address the following safety-related updates and provide guidance to the investigational sites: o Several Pfizer text revisions were incorporated regarding the safety reporting requirements for this study. o Text was added to clarify the SAE reporting timelines for the study and provide guidance regarding the evaluation of and assessment procedures for congenital anomalies. Section 8.10.1: For further clarification, aligned the study assessment window requirements before vaccination to provide guidance and greater logistical convenience for the investigational sites with respect to enrolling participants into the study. Section 8.10.3: Added clarification text with regards to the reporting requirements for maternal participants diagnosed as GBS positive and pregnancy outcome information. This is to improve clarity and consistency with the reporting requirements at investigational sites.

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		Section 8.11.1: Added clarification text on how the infant participant's identifier will be assigned for this study. Sections 8.11.1 to 8.11.6: Added clarification regarding the reporting of standard-of-care measurements for vital sign assessments, measurements, and physical examination procedures (where applicable) to provide greater logistical convenience for the investigational sites to comply with study protocol requirements. Section 9.2 and Section 9.4.1: Modified text to more generally describe Type 1 error control procedures and refer to the SAP for details. Section 9.4.3.2: Added clarification regarding the planned analyses for the healthcare utilization endpoints. Section 10.2.5: Deleted the "SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool" section. For consistency, only the Vaccine SAE Reporting Form process will be used. Appendix 6: Added clarification text to the microbiological data collection requirements for the study based on any pathogen-related assessments/findings performed as part of the participant's routine clinical care. This is to ensure there is some consistency to the source records provided for these events in relation to the protocol requirements and to address regulatory guidance in light of the COVID-19 outbreak or other outbreaks. Appendix 7: Added clarification text to the following: o Incorporated minor editorial revisions into the Schedule of Activities for Maternal Participants Enrolled in the Sentinel Cohort in Japan.

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		o Added clarification text to exclusion criterion 12 regarding the definition of illicit drug use based on country-specific requirements. o Incorporated clarification text regarding the definition of an SAE caused by a medical device. Appendix 9: Added a country-specific appendix for South Korea and Taiwan to address the minimum age requirements for maternal participants in each country. Throughout: Incorporated minor editorial revisions as appropriate.
Protocol amendment 4	22 March 2021	PROTOCOL SUMMARY: Changes were made in the protocol summary to match the revisions made in the main body of the protocol. Section 1.2.3: Added text to address safety reporting requirements during consent/assent for minors enrolled as maternal participants in the study. Section 2.1: Added text to address the enrollment of adolescent menarchal females into the study, ie, no lower age limit for maternal participants. This is based on recent regulatory feedback regarding the study design for RSVpreF evaluation in pregnant adolescent females. Section 3.1 and Section 9.4.1: The secondary and exploratory endpoints were revised to correspond with the planned statistical analyses of RTI events in the pediatric population: o Updated secondary objectives pertaining to hospitalization and MA-LRTI due to any cause, extended the efficacy analysis to be in line with the duration of follow-up for infant participants during the first year of their participation in the study, which is 360 days after birth.

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		o An additional secondary objective added to assess the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV. o An additional exploratory objective added to assess the efficacy of RSVpreF in reducing the incidence of MA-RTI, MA-LRTI, and severe MA-LRTI in premature infants <37 weeks of age. These updates are reflected in the statistical section of the protocol and do not represent a change to the study design but instead better reflect the total statistical analysis plan. Section 4.1: For further clarification, added text to address the consent/assent requirements for minors enrolled as maternal participants in the study. Section 4.1 and Section 4.1.2: Given the COVID-19 pandemic situation, and the variable RSV season, the maternal participant sample size on the study may need to be increased and enrollment could possibly go up to 10,000 maternal participants. Section 4.4: Added text to clarify the study definition for a completed maternal/infant participant in the study. Section 5.1.1: Added clarification with regards to inclusion criteria and incorporated administrative update: o Removed the lower age limit for healthy pregnant females likely to be eligible for enrollment in the study. This change will facilitate recruitment of suitable maternal participants for the study. o Allowed the GA determination to be based upon the first trimester ultrasound examination alone, without the last menstrual period, in countries where this is routine. This is to improve clarity

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		and consistency with the GA determination requirements at the investigational sites. o Updated criterion 4 regarding fetal anomaly ultrasound examination requirements in the study. This is to improve clarity and ensure consistency with study requirements at investigational sites. Section 5.2.1: Incorporated administrative update and clarification with regards to: o Marijuana use and maternal participant eligibility in the study. o The use of licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary, or emergency use based on regulatory and national recommendations in maternal participants enrolled into the study. This was to provide additional clarification to the investigational sites with regards to the eligibility criteria of maternal participants. Section 5.2.3, Section 6.5.1, and Section 6.5.2: Due to the current COVID-19 pandemic, added text to clarify the vaccination delay criteria and nonvaccine administration window for maternal participants receiving licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary or emergency use. This change is consistent with other nonstudy vaccines allowed in the study. Section 6.3.1, Section 8.1.2, Section 8.2.1 to Section 8.2.1.3, Section 8.3, Section 8.3.1, Section 8.3.1.2, Section 8.10.1 to Section 8.10.6, and Section 10.1.3: Added text to clarify the consent/assent requirements during study procedures/assessments in the event “a minor” is enrolled as a maternal participant. This is to improve

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		clarity and ensure consistency for the investigational sites to comply with study protocol requirements. Section 8.3.8.1: Added text to make the following safety-related updates and provide guidance to the investigational sites: o Incorporated safety reporting text for participants who report a positive test result for SARS-CoV-2 during the study. o Text was added to clarify the AESI reporting requirements for the study and provide guidance regarding the definition of and categorization of a developmental delay in infant participants. Section 8.10.1: Incorporated administrative update regarding which body systems are deemed mandatory and which discretionary during physical examination procedures for maternal participants in the study. This is to provide greater logistical convenience for the investigational sites to comply with study protocol requirements. Section 8.11.1: Incorporated text regarding the reporting of standard-of-care measurements for vital sign and physical examination procedures at the infant's birth. This is to provide greater logistical convenience for the investigational sites to comply with study protocol requirements. Section 8.11.7, Section 8.11.8, and Section 8.12: Added text to clarify the nasal swab collection requirements from infant participants during a confirmed MA-RTI episode. This is to provide flexibility and prioritize participant safety during the study. Section 9.3, Section 9.4.2, Section 9.4.3, and Section 9.4.3.2: Added text to clarify the statistical analysis procedures in line with the current revisions.

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		Appendix 7 and Appendix 9: Removed the lower age limit for healthy pregnant females likely to be eligible for enrollment into the study. In addition, incorporated minor editorial revisions to the informed consent document for maternal participants enrolled in Japan only. Appendix 8: Added the Philippines to the list of countries impacted by an extension to the screening period for maternal participants with regard to GA requirements and consent process. Throughout: Incorporated minor editorial revisions as appropriate.
Protocol amendment 5	12 January 2022	PROTOCOL SUMMARY: Changes were made in the protocol summary to match the revisions made in the main body of the protocol. Section 1.1 and Section 3.1: Typographical error with the third secondary efficacy endpoint pertaining to EAC activities was removed to align with the protocol-defined procedures and SAP. Section 5.2.3: Administrative update to clarify the coadministration window requirements for licensed COVID-19 vaccines and COVID-19 vaccines authorized for temporary or emergency use, based on evolving regulatory and national guidelines. Section 6.5.1 and Section 6.5.2: Added text to clarify the coadministration requirements for any licensed vaccines containing pertussis in maternal participants likely to be eligible for the study. Section 1.1, Section 4.1, Section 9.2, Section 9.4.1, and Section 9.5: Modified text to address additional interim analyses planned for the study. Appendix 10: Added a country-specific appendix for South Korea to address marijuana use and maternal participant eligibility in the study.

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		Appendix 11: Added a country-specific appendix for The Philippines at the request of the Philippine Health Research Ethics Board (PHREB) that clarifies the compensation/reimbursement requirements for participants enrolled in the Philippines based on national regulatory laws and recommendations.
Protocol amendment 6	01 June 2022	PROTOCOL SUMMARY: Changes were made in the protocol summary to match the revisions made in the main body of the protocol. Section 1.2.4: Updated the window of assessment for infant physical examination from 48 to 72 hours to reflect the current entry in Section 8.11.1. Section 1.2.4.1: Revisions were made to the schedule of activities for infant participants to clarify language related to RTI assessments. Section 2.2, Section 4.1, and Section 4.1.2: Modified language to justify a new enrollment strategy and endpoint case-accrual plan. Section 5.2.1: Added text to exclusion criterion 11 to clarify that maternal participants who have previously received SARS-CoV-2 monoclonal antibodies as part of their COVID-19 treatment, postexposure prophylaxis, or preexposure prophylaxis are now permitted to be enrolled in the study. Section 9.2, Section 9.4.1, and Section 9.5: Modified text to address final analyses planned for the study. Section 10.1.5: Several Pfizer protocol template text revisions were incorporated pertaining to the dissemination of clinical study data.

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10.14. Appendix 14: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
ADE	adverse device effect
AESI	adverse event of special interest
Al(OH)3	aluminum hydroxide
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
AST	aspartate aminotransferase
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
dLIA	direct-binding Luminex immunoassay
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EAC	endpoint adjudication committee
EACC	endpoint adjudication committee charter
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDD	estimated delivery date
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine

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Abbreviation	Term
GA	gestational age
GBS	group B streptococcal
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HCP	healthcare provider
HDEC	Health and Disabilities Ethics Committee
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPV	human papillomavirus
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
IUI	intrauterine insemination
IV	intravenous
IWR	interactive Web-based response
LFT	liver function test
LMIC	lower- and middle-income country
LMP	last menstrual period
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
N/A	not applicable

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Abbreviation	Term
NAAT	nucleic acid amplification technology
NDCMC	newly diagnosed chronic medical condition
PACL	protocol administrative change letter
PCD	primary completion date
PCR	polymerase chain reaction
PFS	prefilled syringe
PHREB	Philippine Health Research Ethics Board
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
RAD	reactive airway disease
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
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
SADE	serious adverse device effect
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMS	short message service
SoA	schedule of activities
SOP	standard operating procedure
SpO2	oxygen saturation
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
Tdap	tetanus, diphtheria, and acellular pertussis vaccine
TOC	table of contents
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VE	vaccine efficacy

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Document Approval Record

Document Name:	C3671008 Protocol Amendment 7 Clean Copy, 08Aug2022
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

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[redacted]	[redacted]	[redacted]

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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: 1

Date: 28 May 2020

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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. 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.

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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 6 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.
- 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-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.

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).

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- Variable: Occurrence of RSV-positive MA-LRTI 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.
- 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.
- 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 2).
- Intercurrent event(s): No intercurrent events to be considered.
- Population-level summary: Percentage of infant participants with specific birth outcomes in each group.

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- **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.

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- 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.

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- 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, 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 hospitalization 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.
- Population-level summary: RR reduction of hospitalization 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.

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

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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, and 180 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.

- Population-level summary: RR reduction of MA-LRTI due to any cause occurring up to 90 days, 120 days, 150 days, and 180 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 is anticipated that approximately 6900 mother-infant pairs may be needed to accumulate 124 per-protocol cases. Study-eligible pregnant women will be randomized in a 1:1 ratio to receive a single dose of 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.

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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, and 180 days after birth.

- MA-LRTI due to any cause with protocol-defined criteria occurring within 90 days, 120 days, 150 days, and 180 days after birth.

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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 181 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 (as confirmed by the EAC) occurring within 180 days after birth.
- Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits occurring within 180 days after birth.
- 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).
- Mean/median composite score summarizing healthcare utilization, 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.

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.

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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. 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 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 informed consent 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

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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.

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 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.

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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 participant reports the reaction as "yes" for redness or swelling (with a diameter of 2.5 cm or more) **or** "mild," "moderate," "severe," or "Grade 4" for pain at the injection site on a given day;

= "No," if the participant reports the reaction as "no" **or** as "yes" with a diameter of less than 2.5 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)	Participant reports the reaction as "yes" on any day from Day 1 through Day 7.	Participant reports the reaction as "no" on all 7 days or as a combination of "No" and missing on all 7 days.	Participant reports the reaction as missing on all 7 days.

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

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

Table 3. Derived Variables for Any Local Reaction

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

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Grading Scale for Local Reactions

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

Table 4. Grading Scale for Local Reactions

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

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

Maximum Severity for Local Reactions

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

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

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

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

Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction + 1). Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

Onset of Local Reaction

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

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

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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 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

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Table 5. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe nausea
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

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

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

Table 6. Grading Scale for Fever

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

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

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

= "Yes," if the participant reports a temperature ≥38.0°C for fever **or** "mild," "moderate," "severe," or "Grade 4" for the remaining events on a given day.

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

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

1. Presence or absence of each systemic event on each day (Days 1-7) after vaccination.
2. Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
3. 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.

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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.

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 eligible, are born to the maternal participants who did not have major protocol deviations prior to the delivery, received the investigational product to which they were randomized at least 14 days prior to delivery, and have no major protocol deviations.
Modified intent-to-treat (mITT) efficacy – infant	All infant participants who are born to vaccinated maternal participants.

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Population	Description
Evaluable immunogenicity – infant	All infant participants who are eligible, are born to the maternal participants who did not have major protocol deviations prior to the delivery, received the investigational product to which they were randomized, 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 through the data handling memo 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

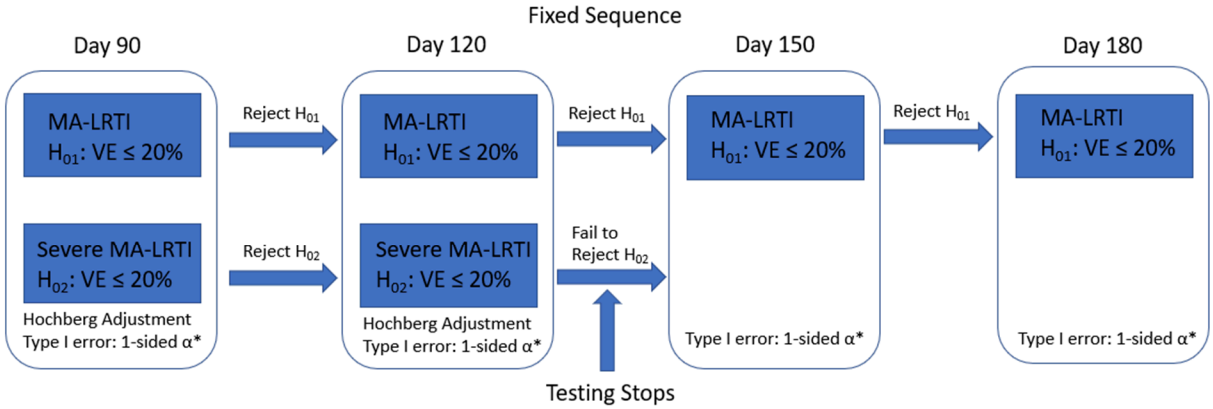
The null hypothesis to be tested concerns VE for the primary endpoints. RSVpreF will be compared to placebo, testing the hypotheses for each endpoint of H_{0i}: VE $\leq$20% vs H_{ai}: VE >20%, where i = 1 denotes the MA-LRTI endpoint and i = 2 denotes the severe MA-LRTI endpoint. The overall primary 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.

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The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV will be tested in parallel using a Hochberg multiplicity adjustment procedure. 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 Hochberg adjustment. If that null hypothesis cannot be rejected, testing ends. Otherwise, testing proceeds with the incidence within 120 days after birth, at the full alpha level. 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.

This testing procedure for the primary endpoints was evaluated for type I error control via simulation. Details are provided in Appendix 1. Simulated cases of MA-LRTI and severe MA-LRTI were generated, each with a true VE of 20% as the limit of the null space. Overall type I error remained below 0.0245 1-sided, the critical level at the final analysis, in all scenarios studied.

Inference for the secondary endpoints will be conditional upon demonstrating success through 180 days for the primary efficacy endpoint. The secondary endpoints of hospitalizations due to RSV and all-cause MA-LRTI 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

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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. Since the 2 secondary endpoints are not closely related (as are the primary endpoints), a Bonferroni multiplicity adjustment will be used to analyze the 2 secondary endpoints in parallel. VE for each secondary endpoint will be evaluated sequentially at 90 days, 120 days, 150 days, and 180 days, as for the primary endpoint. 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.

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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). For calculating a fold rise,

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< 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.

5.4. 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. 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

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Table 8. Endpoint Events and Definitions in Infant Participants

Study Endpoint/Assessment	Study Definition
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
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

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Table 8. Endpoint Events and Definitions in Infant Participants

Study Endpoint/Assessment	Study Definition
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by EAC

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.

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-LRTI = medically attended lower respiratory tract illness; RTI = respiratory tract illness

5.5. Healthcare Utilization Score

Details of the health utilization score calculation will be provided in a future SAP amendment.

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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.
- 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, as confirmed by the EAC, will be presented for each group.
- 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.

A further 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.

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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.
- For each group, the number (n), percentage, and 95% CI of cases of severe MA-LRTI due to RSV occurring within 90 days (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.

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 2 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).

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- 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.

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

6.1.3.2. 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:
  - Presence or absence of each systemic event on each day (Days 1-7) after vaccination.
  - Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.

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- 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.

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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, and 180 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.
- For each group, the number (n), percentage, and 95% CI of cases of hospitalization due to RSV occurring within 90 days 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, 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.

6.2.1.1.2. Supplementary Analysis

The main analysis will also be performed based on the mITT efficacy infant population.

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

6.3. 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).

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- 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.

- For each group, the number (n), percentage, and 95% CI of RSV-positive MA-RTI cases occurring within 90 days 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.

- 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 365 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 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.

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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.
- 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) 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 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.

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- 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.

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 50% 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 50% 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 50% 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 50% 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. Mean/Median Composite Score Summarizing Healthcare Utilization

- Analysis set: Evaluable efficacy – infant (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Details of the health utilization analysis will be provided in a future SAP amendment.

6.3.1.12. IgG Concentrations Against Prefusion F Measured at Birth

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

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- 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.

6.3.2. 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 50% 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 50% 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 50% 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 50% serum neutralizing titers from before vaccination to each available time point after vaccination for each vaccine group.

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- GMRs of the RSV vaccine group to the placebo group for the RSV A and RSV B 50% 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 50% 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 50% 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.

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6.4. Subset Analyses

Table 10 summarizes the defined subgroup analyses. Additional subset analyses (not defined here) may also be performed if deemed necessary.

Table 10. Subgroup Analysis for Infant Participants

Subgroup	Endpoints	Population
Gestational age (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 or >14 days (if sufficient data)	• Primary efficacy endpoints Immunogenicity endpoints	• Evaluable efficacy infant • Evaluable immunogenicity infant
≤30 Days or >30 days	• Primary efficacy endpoints Immunogenicity endpoints	• Evaluable efficacy infant • Evaluable immunogenicity 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 infant • Evaluable efficacy infant
Country subcategories (level of income: low, upper middle, high) (see Appendix 3)	• Primary efficacy endpoints • Immunogenicity endpoints • Pregnancy & birth outcome • Hospitalization due to RSV (up to 730 days)	• Evaluable efficacy infant • Evaluable immunogenicity infant • Safety 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
Time of enrollment (first or second year of the study)	• Demographics	• Safety infant

Abbreviation: RSV = respiratory syncytial virus.

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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), current 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.

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.

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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 separately for maternal and infant participants.

MA-RTI concomitant medications and antibiotic medication 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.

A summary of specific NDCMCs terms will be provided by SOC and PT. These specific terms will be identified by Pfizer clinical personnel on an ongoing basis.

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

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

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

6.6.2. Reactogenicity Data

Analysis and summaries of primary reactogenicity endpoints are described in Section 6.1.3.1 and Section 6.1.3.2.

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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) will be provided in accordance with the Pfizer reporting standards. All summaries and listings for these data will be generated separately for maternal and infant participants.

6.6.4. 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, and ≥34 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.

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. Because of the relatively low number of cases of severe MA-LRTI due to RSV expected, the interim analysis will not consider that endpoint. 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.

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7.2. Interim Analyses and Summaries

There may be a single interim analysis of the MA-LRTI-due-to-RSV endpoint when there is an adequate number of cases (at least half the target number). Based on the fraction of cases included in the interim analysis, an alpha level will be derived based on a Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. For example, if there is a single interim analysis at exactly 50% of the cases, the appropriate 1-sided significance levels are 0.0014 at the interim analysis and 0.0245 at the final analysis. 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 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 the interim analysis is reached, it is possible that additional potential cases will be under adjudication. These additional cases will be included in the interim analysis only if confirmed as cases by the EAC on the same day that the last per-protocol case is confirmed.

Testing at the interim analysis will follow the sequence of interval-specific tests as described in Section 9.4.1 of the protocol. However, consideration will be given to stopping the study for efficacy only if all time intervals through 180 days indicate statistically significant efficacy. Secondary endpoints will not be tested at the interim analysis.

Futility will also be assessed at the interim analysis 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 are 62 cases available for the interim analysis, Table 11 indicates case splits for which stopping the study will be considered. The actual number of cases available may be slightly higher or lower than 62, and the decision rules amended accordingly.

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
62	29	33	12% (-49%, 49%)	Conditional power <20%[b]; possible futility declaration

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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
62	15	47	68% (24%, 88%)	Maximum number of RSV cases permitted to declare VE >20%

Abbreviation: VE = vaccine efficacy.
a. 99.7% confidence level for efficacy declaration; 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.

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

4. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus–associated hospitalizations among children less than 24 months of age. Pediatrics 2013;132(2):e341-8.

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9. APPENDICES

Appendix 1. Multiplicity Correction Strategy

Testing Procedure

As described in Section 5.1, testing of the 2 primary endpoints of MA-LRTI and severe MA-LRTI follows this sequence:

1. Incidence of the 2 endpoints through 90 days after birth will be analyzed. A 1-sided alpha of 2.45% will be applied and a Hochberg multiplicity correction used. If the null hypothesis for both of the primary endpoints cannot be rejected, testing ends.

2. Otherwise, the endpoint(s) for which null hypotheses through 90 days were rejected will proceed to be tested for incidence through 120 days. A 1-sided alpha of 2.45% will be applied. If both endpoints were successful at 90 days and are to be analyzed at 120 days, a Hochberg multiplicity correction will again be used. If neither analysis is successful at 120 days, testing ends, and conclusions are based on the 90-days endpoint results.

3. Otherwise, testing proceeds in the same way at 150 days for those endpoint(s) successful at 120 days; and testing proceeds further in the same way at 180 days for those endpoint(s) successful at 150 days.

Of note, analysis of a given endpoint at later time points is conditional on success at all earlier time points.

Simulation Setup

The study design specifies 124 cases of the MA-LRTI endpoint through 90 days, with an undetermined number of these cases also meeting the criteria for severe MA-LRTI. We explored scenarios where 20%, 30%, 40%, or 50% of the total MA-LRTI cases were severe and analyzed them separately for the second primary endpoint.

Concerning additional cases occurring after 90 days but up to 180 days, there are no specific protocol targets for these. However, an expected number of cases was estimated based on Hall, et al.[4] Calibrating relative incidence in each month of life relative to the target of 124 cases within 90 days from the study population, this resulted in the following estimated numbers of additional cases of MA-LRTI: 24 cases occurring after Day 90 through Day 120; 21 cases occurring after Day 120 through Day 150; and 11 cases occurring after Day 150 through Day 180. The proportions of severe MA-LRTI were assumed to apply beyond 90 days as for the 90-day period.

Trial results were simulated via the transformation between VE θ and the proportion of cases in the vaccine group π. As described in Section 5.2.1, for this trial design with equal numbers of participants assigned to vaccine and placebo, $\pi = (1 - \theta)/(2 - \theta)$. Thus, for an assumed value of VE of 20% or 0.2, the proportion of vaccine cases is (1 - 0.2)/(2 - 0.2), or 0.444. As the largest value of VE in the null space, this value was assumed for both endpoints to identify the highest possible type I error.

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Since severe MA-LRTIs are a subset of MA-LRTIs, the simulation followed these steps:

- The stipulated proportion of severe cases through 90 days was calculated, eg, 20% of 124 = 25 severe cases total.
- The number of severe cases in the vaccine group was generated as B(25, 0.444).
- The number of nonsevere MA-LRTIs through 90 days was derived, eg, 124 - 25 = 99.
- The number of nonsevere cases in the vaccine group was generated as B(99, 0.444).
- Severe and nonsevere cases were added to obtain all MA-LRTIs through 90 days.
- The incremental numbers of MA-LRTIs and severe MA-LRTIs after 90 days through 120 days were similarly generated, and for the subsequent periods also.
- Each endpoint at each interval was analyzed by the exact binomial test, for the null hypothesis that the proportion of vaccine cases was 0.444 or greater. The testing procedure as described in Section 5.1 was applied, and the proportion of successes for either primary endpoint in each time interval tabulated.

Results

Because of the gatekeeping strategy, the proportion of false-positives monotonically decreased with each successive time interval. Even at the 90-day analysis, type I error was strictly less than 2.45% 1-sided, for all scenarios.

	Type I Error (% of Rejections Under $\pi = 0.444$)			
% of Severe	**Day 90**	**Day 120**	**Day 150**	**Day 180**
20%	2.02%	1.48%	1.15%	0.96%
30%	1.96%	1.42%	1.06%	0.94%
40%	1.49%	1.19%	0.85%	0.79%
50%	1.77%	1.34%	0.97%	0.90%

R Code

```
############ RSV Type I Error Simulations ###############
alpha=0.0245
#Null hypothesis
theta.null=0.2                          #Vaccine Efficacy (VE)
h=1                                     #follow-up time ratio (placebo/vaccine)
pi.null=(1-theta.null)/(1+h-theta.null)     #proportion of cases in vaccine group

#Alternative Hypothesis
theta.alt=0.6                          #Vaccine Efficacy (VE)
pi.alt=(1-theta.alt)/(1+h-theta.alt)  #proportion of cases in vaccine group


###### Function to Test Both Endpoints #########
testboth<-function(tm, nsl, sl){
```


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```
if (tm==1){
severe=rbinom(1, case.s[1], piS)
nsevere=rbinom(1, case.ns[1], piNS)
} else {
  severe=rbinom(1, case.s[tm]-case.s[tm-1], piS)+sl
  nsevere=rbinom(1, case.ns[tm]-case.ns[tm-1], piNS)+nsl
}
total=sum(severe, nsevere)

pval.s=pbinom(severe, case.s[tm], pi.null)
pval.t=pbinom(total, case.t[tm], pi.null)

if (pval.s>=pval.t) {order="T"} else {order="S"}
if (max(pval.s, pval.t)<alpha) {pass="Both"} else
  if (min(pval.s, pval.t)<alpha/2) {pass=order} else
  {pass="F"}
return(list(pass=pass, ns=nsevere, s=severe))
}


###### Function to Test One endpoint, either Severe or total #########
testone<-function(tm, test, nsl, sl){
  severe=rbinom(1, case.s[tm]-case.s[tm-1], piS)+sl
  nsevere=rbinom(1, case.ns[tm]-case.ns[tm-1], piNS)+nsl
  total=sum(severe, nsevere)
  if (test=="S") {
     pval.s=pbinom(severe, case.s[tm], pi.null)
    if (pval.s<alpha) {return(list(pass="S", ns=nsevere, s=severe))} else
{return(list(pass="F",stop=tm))}
  } else {
    pval.t=pbinom(total, case.t[tm], pi.null)
    if (pval.t<alpha) {return(list(pass="T", ns=nsevere, s=severe))} else
{return(list(pass="F",stop=tm))}
  }
}


#### Simulations####
#Initial Values
timept<-c(90, 120, 150, 180)
case.t<-c(124, 124+24, 124+24+21, 124+24+21+11)

#Parameters
piNS=pi.null #assumed pi for Non-Severe LRTIs
piS=pi.null  #assumed pi for Severe LRTIs
sevpct=0.2   #percentage of severe cases
case.s=round(case.t*sevpct)
case.ns=case.t-case.s

#simulation start point
results=NULL
Nsimu=50000
set.seed(1234)

for (N in 1:Nsimu)
{
  stop=timept[4]
  tm1r=testboth(tm=1, nsl=0, sl=0)
  if (tm1r$pass=="Both") {tm2r=testboth(tm=2, nsl=tm1r$ns, sl=tm1r$s)} else
    if (tm1r$pass=="S") {tm2r=testone(tm=2, test="S", nsl=tm1r$ns, sl=tm1r$s)} else
      if (tm1r$pass=="T") {tm2r=testone(tm=2, test="T", nsl=tm1r$ns, sl=tm1r$s)} else {
        tm2r=list(pass="F")
        stop=timept[1]}

  if (tm2r$pass=="Both") {tm3r=testboth(tm=3, nsl=tm2r$ns, sl=tm2r$s)} else
    if (tm2r$pass=="S") {tm3r=testone(tm=3, test="S",nsl=tm2r$ns, sl=tm2r$s)} else
      if (tm2r$pass=="T") {tm3r=testone(tm=3, test="T",nsl=tm2r$ns, sl=tm2r$s)} else {
        tm3r=list(pass="F")
        stop=min(timept[2], stop)}
```

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```
  if (tm3r$pass=="Both") {tm4r=testboth(tm=4, nsl=tm3r$ns, sl=tm3r$s)} else
    if (tm3r$pass=="S") {tm4r=testone(tm=4, test="S", nsl=tm3r$ns, sl=tm3r$s)} else
      if (tm3r$pass=="T") {tm4r=testone(tm=4, test="T", nsl=tm3r$ns, sl=tm3r$s)} else {
        tm4r=list(pass="F")
        stop=min(timept[3], stop)}

  result<-c(tm1r$pass, tm2r$pass, tm3r$pass, tm4r$pass, stop)
  results=rbind(results, result)
}

day90=c(1-sum(results[,1]=="F")/Nsimu, sum(results[,1]=="Both")/Nsimu,
sum(results[,1]=="S")/Nsimu, sum(results[,1]=="T")/Nsimu)
names(day90)=c("AnyRej", "Both", "Severe only", "Total only")

day120=c(1-sum(results[,2]=="F")/Nsimu, sum(results[,2]=="Both")/Nsimu,
sum(results[,2]=="S")/Nsimu, sum(results[,2]=="T")/Nsimu)
names(day120)=c("AnyRej", "Both", "Severe only", "Total only")

day150=c(1-sum(results[,3]=="F")/Nsimu, sum(results[,3]=="Both")/Nsimu,
sum(results[,3]=="S")/Nsimu, sum(results[,3]=="T")/Nsimu)
names(day150)=c("AnyRej", "Both", "Severe only", "Total only")

day180=c(1-sum(results[,4]=="F")/Nsimu, sum(results[,4]=="Both")/Nsimu,
sum(results[,4]=="S")/Nsimu, sum(results[,4]=="T")/Nsimu)
names(day180)=c("AnyRej", "Both", "Severe only", "Total only")

AnyRej=sum(((results[, 1]!="F")+(results[, 2]!="F")+(results[, 3]!="F")+(results[,
4]!="F"))>0)/Nsimu
#Rejection at any time point in one simulation, supposed to be the same as rejection rate at
day 90

result.all=rbind(day90, day120, day150, day180)
result.all
```

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Appendix 2. Specific Birth Outcomes

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

- Preterm birth (born at <37 weeks' gestation)
- Extremely preterm birth (<28 weeks' gestation)
- Birth weight 1001 to 2500 g
- Extremely low birth weight (≤1000 g)
- Developmental delay collected on the AE page and identified as such in the DHM
- Neonatal death
- Congenital malformations/anomalies
- Other neonatal problems
- Final Apgar score (at either 1, 5, or 10 minutes) less than 7

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Appendix 3. Income Level by Country

Economy	Code	Income Level Group (as Determined by World Bank[a])
Argentina	ARG	Upper middle income
Australia	AUS	High income
Brazil	BRA	Upper middle income
Canada	CAN	High income
Chile	CHL	High income
Denmark	DNK	High income
Finland	FIN	High income
Gambia, The	GMB	Low income
Japan	JPN	High income
Korea, Republic of	KOR	High income
Mexico	MEX	Upper middle income
Netherlands	NLD	High income
New Zealand	NZL	High income
South Africa	ZAF	Upper middle income
Spain	ESP	High income
Taiwan, China	TWN	High income
United States	USA	High income

a. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

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Appendix 4. List of Abbreviations

Abbreviation	Term
AE	adverse event
Apgar	appearance, pulse, grimace, activity, and respiration
ATC4	Anatomic Therapeutic Chemical classification, Level 4
CI	confidence interval
CRF	case report form
DHM	data handling memo
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
Ig	immunoglobulin
IgG	immunoglobulin G
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
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RR	relative risk
RSV	respiratory syncytial virus
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

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Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
ULOQ	upper limit of quantitation
VE	vaccine efficacy
VRD	Vaccine Research & Development
WHO	World Health Organization

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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

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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.

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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

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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

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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.

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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.

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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.

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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.

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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.

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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.

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- 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.

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- **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.

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- 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.

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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.

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- **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.

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- **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.

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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).

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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.

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- 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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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).

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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.

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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

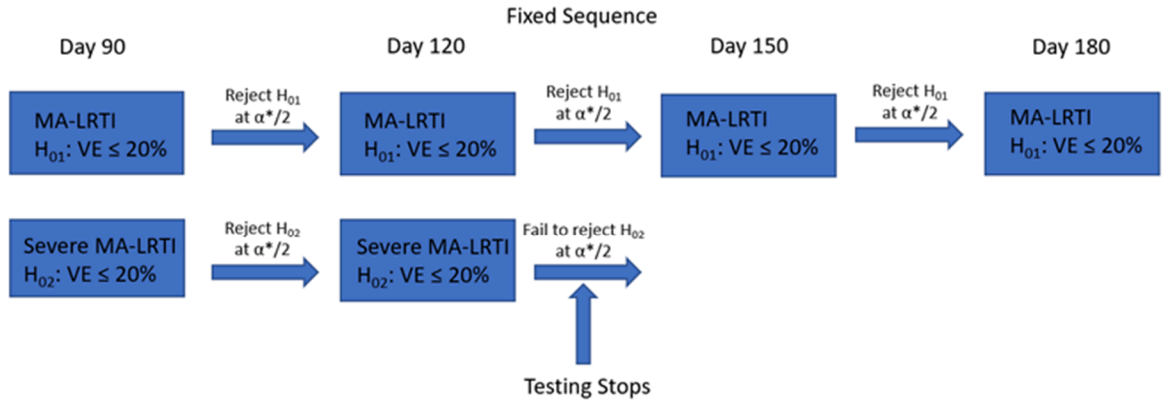
The null hypothesis to be tested concerns VE for the primary endpoints. RSVpreF will be compared to placebo, testing the hypotheses for each endpoint of H_{0i}: VE $\leq$20% vs H_{ai}: VE >20%, where i = 1 denotes the MA-LRTI endpoint and i = 2 denotes the severe MA-LRTI endpoint. The overall primary 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.

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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.

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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.

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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.

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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.

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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

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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.

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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.

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- 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.

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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.

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- 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.

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- 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.

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- 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.

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- 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.

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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.

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- 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.

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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.

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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.

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- 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.

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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.

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- 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.

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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.

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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.

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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.

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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.

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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

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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.

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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

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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

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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

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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
[redacted]	[redacted]	[redacted]

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