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

Investigational Product Number:	PF-06928316
Investigational Product Name:	Respiratory Syncytial Virus (RSV) Vaccine
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3671003
Phase:	2b

Short Title: A Phase 2b 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

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 2	23 October 2019	• Added a country-specific appendix for Argentina, in response to a board of health request for the upper age limit for maternal participants to be 39 years.
Amendment 1	18 June 2019	• Increased the number of participants to up to 650 throughout, as up to 150 participants will be randomized in the southern hemisphere. • Expanded the gestational age of maternal participants to between ≥24 0/7 and ≤36 0/7 weeks at the time of vaccination. • Added a statement that enrollment will be monitored to help ensure distribution of maternal participants across the gestational age range. • Removed the 1-week follow-up visit for maternal participants and updated associated study endpoints, stopping rule, procedures, and assessments throughout, as appropriate, in order to reduce the burden on maternal participants. • Removed the 1-month postdelivery and 12-month postdelivery blood draws for serologic assessment for maternal participants and updated associated study endpoints in order to reduce the burden on maternal participants. • Removed the calculation of body mass index (BMI), as height and weight will be entered in the case report form (CRF). • Updated the route of the temperatures taken for infant participants to rectal throughout, as appropriate, as requested by the Center for Biologics Evaluation and Research (CBER). • Removed the 12-month postdelivery visit blood draws for serologic assessment for infant participants and updated associated study objectives and endpoints and procedures, as appropriate, in order to reduce the burden on infant participants. CCI [redacted]

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		CCI [redacted] • Removed reference to RSV vaccine study arms' being dropped in Section 4.1, as no vaccine study arms will be dropped. • Added a statement to Section 4.1 that the study will be conducted in more than 1 geographic location. • Clarified that calculation of gestational age must be based upon ultrasound results obtained at ≥18 weeks of pregnancy in Section 5.1.1, as requested by CBER. • Clarified that if an ultrasound examination is not performed at ≥18 weeks of pregnancy as standard of care, then an ultrasound examination must be performed and reviewed as part of the screening visit in the schedule of activities, Section 5.1.1, and Section 8.10.1.1. • Added clarification that the stopper on the water-for-injection vial may contain latex. • Added clarification that exclusion criterion 7 applies to current and previous pregnancies. • Updated text to align time periods for recording concomitant medications with those for reporting adverse events (AEs) for maternal and infant participants in Section 6.5.3, Section 6.5.5, and throughout, as required. CCI [redacted] • Clarified that the back and genitourinary body systems must be assessed as part of the infant physical examination in Section 8.10.2 and throughout, as required. • Reduced the total volume of blood collected for both maternal and infant participants in Section 8.2.13. CCI [redacted]

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		CCI [redacted] • Added subgroup analyses of the secondary CCI [redacted] immunogenicity endpoints, including an analysis based on gestational-age subcategories in Section 9.4.1.1, as requested by CBER. • In Section 9.5.1, clarified that additional analyses may be performed at any time during the study and that they may be based on fewer than the total planned number of participants in order to allow earlier analysis of data. • Added the definition of a medically attended adverse event to Section 10.3.
Original protocol	11 March 2019	N/A

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).

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LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

This is a Phase 2b, multicenter, randomized, placebo-controlled study in which up to 650 healthy pregnant women 18 through 49 years of age will be randomized to receive one of 2 dose levels of bivalent (respiratory syncytial virus [RSV] A and B) respiratory syncytial virus stabilized prefusion F subunit vaccine (RSV vaccine) at 120 µg (60 µg A and 60 µg B) and 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, formulated with or without aluminum hydroxide (Al[OH]$_3$), or placebo (1:1:1:1:1 randomization). Assessments will include descriptions of safety, tolerability, and immunogenicity in maternal participants as well as safety and characteristics of transplacentally transferred antibodies in their infants.

CCI [redacted]

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

Approximate Duration of Participant Participation

Pregnant women will participate in the study from enrollment during their pregnancy, and for approximately 12 months after delivery of their newborn infants.

Pregnant women will be vaccinated at a time of year such that the infant is likely to be exposed to RSV during the first 6 months of life.

Infants will participate from birth to approximately 12 months of age.

Approximate Number of Participants

Up to 650 healthy pregnant women will be randomized. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 and ≤36 0/7 weeks.

Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

- The active ingredients in the RSV vaccine are 2 stabilized prefusion RSV F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The vaccine is supplied as a lyophilized cake that is reconstituted by diluent with either sterile water for injection or a sterile suspension of Al(OH)$_3$ in water for injection.

Placebo

- The placebo for RSV vaccine will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

Data Monitoring Committee

This study will use an IRC and an E-DMC.

Statistical Methods

There is no statistical hypothesis specified in this study. The primary objectives are to describe the safety and tolerability of 2 dose levels of RSV vaccine candidate with or without $Al(OH)_3$ in maternal participants and to assess the safety of maternal immunization in infant participants born to women 18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy. The safety populations will be used to evaluate the primary objectives.

Safety data will be analyzed separately for maternal participants and infant participants. Maternal participants will be analyzed according to the investigational product received, and infant participants will be analyzed according to the investigational product their mothers (maternal participants) received.

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.

All safety and immunogenicity analyses will be descriptive in nature.

An analysis will be performed when the delivery-visit RSV-neutralizing antibody titer data from all maternal and infant participants and the 1-month-after-birth visit data for infant participants are available. A further analysis will be performed when all data are available from the infant participants' 6-month visit. Additional analyses may be conducted before the final analysis to support internal program-level decisions as needed.

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

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA tables provide 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.

1.3.1. Schedule of Activities for Maternal Participants

Visit Description	**Screening (Visit 0)**	**Vaccination**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**Delivery**	**1-Month Postdelivery Visit**	**6-Month Postdelivery Visit**	**12-Month Postdelivery Visit**
Visit Window (Days)	**Day -14 to Day -2 Prior to Vaccination**[a]	**Day 1**	**14 to 17 Days After Vaccination**[b]	**28 to 42 Days After Vaccination**[b]	**Varies**	**28 to 35 Days After Delivery**	**168 to 210 Days After Delivery**	**350 to 378 Days After Delivery**
Informed consent	X							
Assign single maternal participant identifier	X							
Demography	X							
Record current alcohol, tobacco, and marijuana usage	X							
Medical history including obstetric history[c]	X							
Record LMP and EDD	X							
Vital signs[d]	X	X	X	X				
Physical examination	X							
Measure weight and height	X							
Measure weight		X	X	X				
Obstetric examination	X	X	X	X				
Record baseline concomitant medication	X							
Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions, or Rho(D) immune globulin	X	X	X	X	X	X	X	X
Record nonstudy vaccine information	X	X	X	X	X	X	X	X
Review eligibility criteria	X							
Blood draw for hematology and blood chemistry assessments	X							
Review laboratory results for hematology and chemistry assessments[e]		X						
Blood draw for HBV, HCV, HIV, and syphilis testing	X							
Review results from HBV, HCV, HIV, and syphilis testing[e]		X						
Review temporary delay criteria		X						
Review continued eligibility		X	X	X	X			
Blood draw for serologic assessment (~25 mL per blood sample)		X	X	X	X		X	

Visit Description	Screening (Visit 0)	Vaccination	2-Week Follow-up Visit	1-Month Follow-up Visit	Delivery	1-Month Postdelivery Visit	6-Month Postdelivery Visit	12-Month Postdelivery Visit
Visit Window (Days)	**Day -14 to Day -2 Prior to Vaccination[a]**	**Day 1**	**14 to 17 Days After Vaccination[b]**	**28 to 42 Days After Vaccination[b]**	**Varies**	**28 to 35 Days After Delivery**	**168 to 210 Days After Delivery**	**350 to 378 Days After Delivery**
Urine sample for glucose and protein testing	X	X						
Assign randomization and container number		X						
Administer investigational product		X						
Postvaccination observation[f] and assessment of immediate adverse events		X						
Dispense e-diary, digital thermometer, and measuring device[g]		X						
Review and/or collect e-diary[h]			X					
Record pregnancy outcome information					X			
Record concomitant medication taken to treat an adverse event		X	X	X	X	X	X	X
Record adverse events, medically attended adverse events, and serious adverse events, as appropriate[i]	X	X	X	X	X	X	X	X
Surveillance reminder contact					Contact the maternal participant approximately every week until approximately 6 months after delivery			

Abbreviations: EDD = estimated delivery date; e-diary = electronic diary; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LMP = last menstrual period.

Visit Description	Screening (Visit 0)	Vaccination	2-Week Follow-up Visit	1-Month Follow-up Visit	Delivery	1-Month Postdelivery Visit	6-Month Postdelivery Visit	12-Month Postdelivery Visit
Visit Window (Days)	**Day -14 to Day -2 Prior to Vaccination[a]**	**Day 1**	**14 to 17 Days After Vaccination[b]**	**28 to 42 Days After Vaccination[b]**	**Varies**	**28 to 35 Days After Delivery**	**168 to 210 Days After Delivery**	**350 to 378 Days After Delivery**

a. Screening may take place on Day -1 (1 day prior to vaccination) if all laboratory results are available for review prior to vaccination.
b. The 2-week follow-up and 1-month follow-up visits will not be performed if delivery occurs before the visits. Once delivery occurs, the visit windows are calculated based on the delivery date.
c. Where an obstetric ultrasound examination is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination and record findings.
d. Vital signs include oral temperature, seated blood pressure, and heart rate.
e. Laboratory results should be reviewed as soon as they are available.
f. The first 5 maternal participants in the study will be observed for at least 4 hours after investigational product administration. Further vaccination will commence no sooner than 48 hours after the fifth maternal participant received her vaccination. All other maternal participants will be observed for at least 30 minutes.
g. Maternal participants will record (in an e-diary) reactogenicity events each evening for 7 days following vaccination. Remind maternal participants that study staff 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 visit is required.
h. Designated 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.
i. The investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through 1 month after vaccination. From 1 month after vaccination until the maternal participant completes the study, MAEs and SAEs will be collected.

1.3.2. Schedule of Activities for Infant Participants

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Visit Description	**Birth**	**1-Month Follow-up**	**2-Month Follow-up**	**4-Month Follow-up**	**6-Month Follow-up**	**12-Month Follow-up**
Visit Window (Days)	**Birth to 7 Days After Birth**	**28 to 35 Days After Birth**	**49 to 63 Days After Birth**	**112 to 126 Days After Birth**	**168 to 210 Days After Birth**	**350 to 378 Days After Birth**
Assign infant participant identifier	X					
Demography	X					
Collect background factors	X	X	X	X	X	X
Collect birth outcome information (including Ballard score)	X					
Vital signs[a]	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
Length, head circumference, and weight[b,c]	X	X	X	X	X	X
Record nonstudy vaccine information	X	X	X	X	X	X
Record monoclonal antibodies (eg, Synagis) or blood transfusions (eg, whole blood, packed cells)	X	X	X	X	X	X
Review eligibility	X					
Cord blood sample[c] (~10 mL) for serologic assessment	X					
Blood draw for serologic assessment (up to 5 mL per blood sample based on weight)[b]		X	X	X	X	
Record concomitant medication taken to treat an AE	X	X	X	X	X	X
Record adverse events, medically attended adverse events, serious adverse events, and adverse events of special interest, as appropriate[d]	X	X	X	X	X	X

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Visit Description	**Birth**	**1-Month Follow-up**	**2-Month Follow-up**	**4-Month Follow-up**	**6-Month Follow-up**	**12-Month Follow-up**
Visit Window (Days)	**Birth to 7 Days After Birth**	**28 to 35 Days After Birth**	**49 to 63 Days After Birth**	**112 to 126 Days After Birth**	**168 to 210 Days After Birth**	**350 to 378 Days After Birth**
Surveillance reminder contact	After delivery, contact the infant participants' parents approximately every week until approximately 6 months after delivery					

a. Vital signs include rectal temperature, heart rate, oxygen saturation by pulse oximetry **(Visit 1 only)**, and respiratory rate.

b. Infant participants will be randomly assigned to 1 of 2 blood sampling schedules. Blood samples will be collected either at Visit 2 (1-month follow-up) and Visit 4 (4-month follow-up) **OR** at Visit 3 (2-month follow-up) and Visit 5 (6-month follow-up). Weight will be used to determine the volume of blood that can be collected.

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 venous blood sample may be collected from the infant participant up to 24 hours after birth. The infant's weight must be used to determine the volume of blood that can be collected.

d. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") begins at birth and continues through and including a minimum of 28 days after birth. From Visit 2 until the last study visit, only AEs of special interest, MAEs, and SAEs, including hospitalizations, will be reported.

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2. INTRODUCTION

Prevention of RSV disease in young infants is a significant unmet vaccine need globally. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in very young infants, in infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems.[1] Worldwide, RSV kills up to 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 developing countries.[2,3] 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.[4,5] There is increasing evidence that the link between severe RSV disease in infancy and wheezing later in childhood may be causal.[6,7] 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.[8] Infection is essentially universal by the time children reach 2 years of age.[9]

Currently, there is neither specific treatment of 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.[10] Limitations of its use include its high cost[11] and requirement of multiple monthly injections,[12] and so it remains recommended for use only in very premature infants and others at increased risk of severe illness.[5,13]

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.[14] 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,[15,16,17,18,19,20] suggesting that maternal immunization is a reasonable approach to RSV disease prevention among young infants.

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

The RSV vaccine is being developed to prevent medically significant RSV-associated LRTI in infants by active immunization of pregnant women.

2.1. Study Rationale

There is a large medical need for 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 the candidate vaccine. This Phase 2b study will be the first study of the vaccine in pregnant women and their infants and will serve as a proof-of-concept (POC) study for the RSV maternal immunization program, allowing Pfizer to proceed to Phase 3. CCI [redacted]

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).[21] Infants born prematurely and those with underlying cardiac or pulmonary disease are at further increased risk of severe clinical disease due to RSV. A recent 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 country (LMIC) settings, as well as in industrialized nations.[2,3]

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 ideal, 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 revived in early 2014 based on a new scientific discovery (determination of the prefusion F crystal structure)[22] 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. Pfizer has used the National Institutes of Health prefusion RSV F crystal structure to guide the development of a stabilized prefusion RSV F vaccine candidate. The core hypothesis underlying Pfizer's RSV vaccine development effort for prevention of infant disease is that vaccine antigens based on prefusion F, when administered to pregnant women in the second or third trimester of pregnancy, will elicit sufficiently high neutralizing antibody titers to protect against RSV disease via transplacental transfer of antibody to the fetus. Such antibody would then persist above a given threshold to help protect infants early in life, when they are most at risk for severe RSV disease.

2.3. Benefit/Risk Assessment

Pfizer's stabilized prefusion F subunit bivalent RSV vaccine 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).[23] 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.[24] During preclinical studies, in a standard cotton rat infectious RSV challenge model, FI-RSV showed pathological signs of causing disease enhancement, and the Pfizer vaccine candidate did not (investigational new drug application [IND] Module 2.4). 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.[25]

Vaccination with the prefusion RSV F antigens is anticipated to elicit a higher ratio of neutralizing to nonneutralizing antibodies, more closely matching the profile in naturally exposed individuals. The anticipated safety profile of Pfizer's RSV stabilized prefusion F subunit vaccine is expected to be similar to prior postfusion F subunit vaccines tested in RSV-experienced adults.

It is possible that vaccination may provide benefit to the pregnant women who receive it, but potential benefit to the mother will not be evaluated 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 adverse events (AEs) of RSV vaccine may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. Maternal Participant

Primary Objective Maternal Participant	Estimands	Primary Endpoints Maternal Participant
To describe the safety and tolerability of an RSV vaccine	In maternal participants receiving 1 dose of investigational product: • The percentage of maternal participants reporting local reactions • The percentage of maternal participants reporting systemic events • The percentage of maternal participants reporting AEs • The percentage of maternal participants reporting obstetric complications, medically attended AEs (MAEs), and serious adverse events (SAEs)	• Prespecified local reactions within 7 days after vaccination • Prespecified systemic events within 7 days after vaccination • AEs from the time of vaccination through 1 month after vaccination • Obstetric complications, MAEs, and SAEs throughout the study
Secondary Objective Maternal Participant	**Estimands**	**Secondary Endpoints Maternal Participant**

To describe the immune responses elicited by an RSV vaccine	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 geometric mean titer (GMT) for RSV A– and RSV B–neutralizing antibody titers.
	• The immune response, estimated by the geometric mean fold rise (GMFR) from baseline in RSV A– and RSV B–neutralizing antibody titers.
	• Geometric mean ratio (GMR), estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group and the placebo group.
		• RSV A– and RSV B–neutralizing antibody titers measured:
		  • before vaccination
		  • 2 weeks after vaccination
		  • 1 month after vaccination
		  • at delivery

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3.2. Infant Participant

Primary Objective Infant Participant	Estimands	Primary Endpoints Infant Participant
To assess the safety of maternal immunization in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy	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 • The percentage of infant participants having SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs	• Specific birth outcomes • AEs from birth to 1 month of age • SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs through 12 months of age • Congenital anomalies (defined as structural or functional anomalies [eg, metabolic disorders] that occur during intrauterine life and can be identified prenatally, at birth or later in life[26])

Secondary Objective Infant Participant	Estimands	Secondary Endpoints Infant Participant

To describe RSV antibody levels in infants born to women ≥18 through ≤49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy	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
	• GMR, estimated by the ratio of the GMTs for RSV A– and RSV–B neutralizing antibody titers of the RSV vaccine group and the placebo group
		• RSV A– and RSV B–neutralizing antibody titers measured at:
		  • birth
		  • 1 month
		  • 2 months
		  • 4 months
		  • 6 months
		
		Note: Infant participants will be randomly assigned to 1 of 2 blood sampling schedules.

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4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study in which up to 650 healthy pregnant women ≥18 and ≤49 years of age will be randomized to receive one of 2 dose levels of bivalent (RSV A and B) RSV vaccine candidate at 120 µg (60 µg A and 60 µg B) and 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, formulated with or without $Al(OH)_3$, or placebo (1:1:1:1:1 randomization). Assessments will include descriptions of safety, tolerability, and immunogenicity in maternal participants as well as safety and characteristics of transplacentally transferred antibodies in their infants. CCI [redacted] Vaccination of mothers will occur at a time of year such that the infant is likely to be exposed to RSV during the first 6 months of life. The first 5 maternal participants vaccinated in the study will be observed for at least 4 hours after investigational product administration for any acute reactions. Dosing of the remaining maternal participants will commence no sooner than 48 hours after the fifth maternal participant received her vaccination. The immediate postvaccination observation period for all maternal participants after the first 5 will be at least 30 minutes.

It is anticipated that this study may be conducted in more than 1 geographic location including sites in both the northern and southern hemispheres. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 and ≤36 0/7 weeks.

This study will use stopping rules. An IRC and an E-DMC will monitor safety in this study (see Section 9.5.2).

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 12 months after delivery of their infants. The total duration will be up to approximately 17 months depending on gestational age at the time of vaccination. Infants will participate from the time of birth and for approximately 12 months after birth.

Pregnant women will be vaccinated at a time of year such that the infant is likely to be exposed to RSV during the first 6 months of life.

4.1.2. Approximate Number of Participants

Up to 650 healthy pregnant women will be randomized. Approximately 500 women will be randomized in the northern hemisphere and up to 150 additional women will be randomized in the southern hemisphere. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 and ≤36 0/7 weeks.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1.

4.3. Justification for Dose

The doses of vaccine that will be used in this study were determined following assessment of safety and immunogenicity data from the first-in-human (FIH) study, Study C3671001.

The FIH study is designed to describe the safety, tolerability, and immunogenicity of up to 6 different RSV vaccine 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 prefusion RSV 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). Female and male study participants of 2 age groups 18 through 49 years of age and 50 through 85 years of age are being enrolled into both cohorts. The age groups are being run in parallel.

An interim analysis of the sentinel data from the FIH study shows a trend toward increasing neutralizing antibody responses for RSV A and RSV B antigens with increasing dose 2 weeks and 1 month after vaccination. The dose response is most apparent when comparing the 120-µg and 240-µg doses, and the highest vaccine responses are generally observed in study participants who received the highest antigen dose, particularly in those who received 240 µg of antigen with $Al(OH)_3$. Of note, with small numbers of participants in each group (11 or 12), there is still considerable variability. The initial safety data show a benign overall safety profile and no dose response in local reactions, systemic events, or AEs.

The proposed 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. Based on the totality of preclinical and clinical data obtained to date, and given the absence of any sign of dose response in measures of safety or reactogenicity in the FIH study, it is proposed to test 120-µg and 240-µg antigen doses of the bivalent RSV vaccine candidate, with and without $Al(OH)_3$, in pregnant women. These doses are expected to provide the greatest potential level of transplacental antibody transfer to infants and, therefore, the greatest potential benefit.

4.4. End of Study Definition

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1. Inclusion Criteria – Maternal Participants

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, and whose fetus has no significant abnormalities observed on ultrasound.

   Note: Gestational age must be based upon ultrasound results obtained at ≥18 weeks of pregnancy.

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.

4. Had an ultrasound performed at ≥18 weeks of pregnancy.

   Note: Where an obstetric ultrasound is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, an ultrasound must be performed and reviewed as part of the screening visit.

5. Had a negative urinalysis for protein and glucose at the screening visit (Visit 0). Trace protein in the urine is acceptable if the blood pressure is also normal.

6. Determined by medical history, physical examination, screening laboratory assessment, and clinical judgment to be appropriate for inclusion in the study.

7. Expected to be available for the duration of the study, can be contacted by telephone during study participation, and is willing to give informed consent for her infant to participate in the study.

8. Documented negative human immunodeficiency virus (HIV) antibody, hepatitis B virus (HBV) surface antigen, hepatitis C virus (HCV) antibody, and syphilis tests at the screening visit (Visit 0).

Weight:

9. Body mass index (BMI) of <40 kg/m^2 at the time of the screening visit.

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.

5.1.2. Inclusion Criteria – Infant Participants

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

    - The maternal participant must participate in the informed consent process and sign and date an ICD for herself and her fetus/infant prior to the maternal participant's taking part in the study. Informed consent will be obtained from the father of the fetus/infant if mandated by local requirements.

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

5.2. Exclusion Criteria

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

5.2.1. Exclusion Criteria – Maternal Participants

Medical Conditions:

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

2. 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.

3. History of latex allergy.

4. History of any severe allergic reaction (eg, anaphylaxis).

5. Participants with known or suspected immunodeficiency.

6. Current pregnancy resulting from in vitro fertilization or other assisted reproductive technology.

7. A prior history of or known current pregnancy complications or abnormalities that will increase the risk associated with the participant's participation in and completion of the study, including but not limited to the following (refer to the study reference manual [SRM] for further details):

   - Gestational hypertension or preeclampsia-eclampsia
   - Placental abnormality
   - Polyhydramnios or oligohydramnios
   - Significant bleeding or blood clotting disorder
   - Gestational diabetes
   - Any signs of premature labor with the current pregnancy
   - Prior stillbirth or neonatal death, prior low-birth-weight or preterm delivery, prior history of 3 or more miscarriages, prior pregnancies numbering greater than 5, or previous infant with a known genetic disorder or major congenital anomaly

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

9. Participant with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

10. 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:

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

12. Participants who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids (such as for cancer or an autoimmune disease), or planned receipt of such treatment or agents during study participation. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

13. Current alcohol abuse or illicit drug use.

14. Receipt of blood or plasma products or immunoglobulin, 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:

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

Diagnostic Assessments:

16. Laboratory test results at the screening visit outside the normal reference value for pregnant women according to their trimester in pregnancy.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale[28]) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

Other Exclusions:

17. 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.

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

19. Participants who are breastfeeding at the time of the screening visit.

5.2.2. Exclusion Criteria – Infant Participants

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

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.

5.2.3.1. Criteria for Temporarily Delaying Vaccine Administration – Maternal Participants

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

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

- Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 30 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 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 SAE.

Individuals 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.

6.1. Study Intervention(s) Administered

For this study, the investigational product(s) are RSV vaccine and placebo (saline control).

6.1.1. Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

Each lyophilized vial of the RSV vaccine drug product will be supplied as a mixture of equal quantities of 2 stabilized prefusion RSV F antigens, 1 from each of the RSV subgroups A and B in a lyophilized cake.

The lyophilized drug product contains excipients which, after reconstitution, will yield a solution as detailed in Table 1 below.

There are 2 different presentations of RSV drug product representing 2 different dose levels of RSV antigen (120 µg and 240 µg). The lyophilized cake is reconstituted by diluent with either sterile water for injection or a sterile suspension of $Al(OH)_3$ in water for injection. The stopper of the sterile water for injection vial may contain natural rubber latex.

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

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6.1.2. Placebo

The placebo will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

Placebo will be provided by the sponsor to each study site. 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 in accordance with the study's SoA. The investigational product will be administered intramuscularly by injecting 0.5 mL into the deltoid muscle of the nondominant arm by the 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).

6.2. Preparation/Handling/Storage/Accountability

- 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.

- 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.

- 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.

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

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

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

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

- 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.

- 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 unblinded site personnel according to the IP manual. The investigational product will be administered to maternal blinded participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Blinding of Study Site Personnel

This is an observer-blinded study, as the physical appearance of the RSV vaccine and placebo may differ.

The maternal participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

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.

6.3.2. Blinding of the Sponsor

The sponsor study team members will be blinded until the first planned analysis event (see Section 9.5.1).

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

Certain sponsor personnel not directly involved in the conduct of the study will review unblinded data as defined in the IRC charter. Unblinded sponsor personnel who are not part of the study team will be assigned to assess whether a stopping rule is triggered and to conduct ongoing safety review.

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

Investigational product will be dispensed at the study visits summarized in the SoA.

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

Maternal participants will be assigned to receive investigational product according to the randomization scheme. Investigators will remain blinded to each maternal participant's assigned investigational product throughout the course of the study. In order to maintain this blind, 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 following randomization.

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.

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

6.3.4. Breaking the Blind

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. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. 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 Treatments – Maternal Participants

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

- Blood/plasma products or immunoglobulins (except Rho(D) immune globulin [eg, RhoGam], which can be given at any time) and immunosuppressive therapy are prohibited during the course of the study.

- Nonstudy vaccines may not be given concomitantly with the investigational product or within 6 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 Treatments – Maternal Participants

- Licensed vaccines (including influenza 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, pandemic), influenza vaccine, Tdap, or other vaccines may be given at any time.

- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are 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.
- The use of prophylactic antipyretic medication, while permitted, is not recommended on the day prior to vaccination or the day of the investigational product administration.

6.5.3. Recording Nonstudy Vaccinations and Concomitant Medications – Maternal Participants

Details of any medications taken at enrollment will be collected and recorded in the CRF. Medication taken to treat AEs from the signing of the ICD until 1 month after vaccination will be recorded in the CRF. In addition, any medication to treat MAEs or SAEs from 1 month after vaccination until the final study visit will be recorded in the CRF.

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

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

6.5.4. Permitted Concomitant Treatments – Infant Participants

- Routine treatments (including 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.

6.5.5. Recording Nonstudy Vaccinations and Concomitant Medications – Infant Participants

Details of any vaccinations, monoclonal antibodies (eg, Synagis), or blood transfusions (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.

Details of any medication taken to treat AEs from the time of birth until Visit 2 will be recorded in the CRF. In addition, any medication taken to treat AEs of special interest, MAEs, or SAEs from Visit 2 until the final study visit will be recorded in the CRF.

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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, their 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.

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. 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) (if applicable) and reschedule the missed visit as soon as possible and counsel the participant or parent(s) and/or legal guardian(s) (if applicable) on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant or parent(s) and/or legal guardian(s) (if applicable) 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, or parent(s) and/or legal guardian(s) (if applicable) (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) (if applicable) 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 maternal participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all maternal participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

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

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[redacted]

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.

Medical history, physical examination, and assessment of eligibility will be performed on all maternal participants before randomization. In addition, prespecified local reactions and systemic events will be collected from maternal participants for 7 days after vaccination. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2 and Section 8.2.3.

The first 5 maternal participants vaccinated in the study will be observed for at least 4 hours after investigational product administration for any acute reactions. Dosing of the remaining maternal participants will commence no sooner than 48 hours after the fifth participant received her vaccination; the immediate postvaccination observation period for these participants will be at least 30 minutes.

A physical examination and measurement of vital signs will be performed on all infant participants at each visit.

Significant medical history and observations from the physical examination will be documented in the CRF. In addition, AEs, MAEs, and SAEs are collected, recorded, and reported as defined in Section 8.3.3 and Section 10.3.3. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

8.2.1. Electronic Diary – Maternal Participant

The maternal participant will be asked to monitor and record local reactions, systemic events, and fever each evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). The electronic diary (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.

Data on local reactions and systemic events recorded on 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. However, 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.

Investigators (or appropriately qualified designees) are required to review the e-diary data online to evaluate maternal participant compliance and as part of the ongoing safety review (see Stopping Rules in Section 8.2.5).

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.

8.2.2. Local Reactions – Maternal Participants

Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), maternal participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 2. 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.

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. 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 10.3.3).

Site staff will educate the maternal participant regarding signs and symptoms (including necrosis at the injection site or exfoliative dermatitis) that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

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. The investigator will enter this additional information in the maternal participant's source notes and CRF.

Table 2. 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 intensity grading scale. The assessment will be collected on the AE case report form.

8.2.3. Systemic Events – Maternal Participants

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. The symptoms will be assessed by the maternal participant according to the grading scale in Table 3 below. Maternal participants will also be instructed to contact site staff if they experience any Grade 3 prompted systemic event or 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. Study staff may also contact the maternal participant to obtain additional information on events entered into the e-diary.

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. If a maternal participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. The procedure for notification of the sponsor is provided in the study documentation. Grade 4 reactions will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

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. The investigator will enter this additional information in the CRF.

Table 3. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe nausea
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

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

8.2.4. Fever – 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 daily 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. 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.

In the event of a fever on Day 7, 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°F (>38.9°C) will be prompted to contact the investigator. The investigator or 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 4 below. Temperatures reported in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting.

Table 4. 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

8.2.5. Stopping Rules – Maternal Participants

Hematology, blood chemistry, AE data, and e-diary reactogenicity data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

If it is suspected that a stopping rule has been met based on blinded safety assessment, the sponsor's designated unblinded personnel will decide whether a stopping rule has been met based on unblinded randomization information.

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

- The IRC will review all appropriate data.
- The stopping rule will PAUSE all randomization and vaccination.
- The E-DMC will be informed.
- All other routine study conduct activities including, ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following events occur after administration of the investigational RSV vaccine. E-diary data confirmed by the investigator as being entered by the maternal participant in error will not contribute toward a stopping rule.

- If any RSV-vaccinated participant develops an SAE that is assessed as possibly related, or for which there is no alternative, plausible, attributable cause.
- If any RSV-vaccinated maternal participant develops a Grade 4 local reaction or systemic event within 7 days after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
- If any RSV-vaccinated maternal participant develops a fever >104.0°F (>40°C), within 7 days after vaccination, that lasts for at least 24 hours and is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
- If any RSV-vaccinated maternal participant experiences any of the following within 7 days after vaccination: severe vaginal bleeding (eg, partial abruption); severe preeclampsia; eclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; life-threatening sequelae of preeclampsia (eg, pulmonary edema), stillbirth, or fetal loss. Refer to the SRM for further details.
- If ≥2 RSV-vaccinated maternal participants experience premature labor or premature rupture of membranes within 14 days after vaccination.
- If ≥4 RSV-vaccinated maternal participants report the same or similar severe (Grade 3) AE within 7 days after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

8.2.5.1. Enrollment and Vaccination After a Stopping Rule Is Met

Once the IRC has reviewed the safety data and has provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.6. Physical Examinations – All Participants

Maternal Participants: The physical examination 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 (screening visit only) and weight will also be measured and recorded.

The obstetric examination will include, but is not limited to, scars from previous deliveries, fundal height, fetal heart tones, and fetal movement.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Infant Participants: The physical examination 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.

8.2.7. Vital Signs – All Participants

Maternal Participants: Oral temperature, seated blood pressure, and heart rate will be assessed.

- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Infant Participants: Rectal temperature, heart rate, and respiratory rate will be assessed at all visits; additionally, oxygen saturation by pulse oximetry will be assessed at Visit 1 CCI [redacted] All attempts should be made to help ensure that measurements are taken while the infant is resting quietly.

- Heart rate measurements may be assessed with a completely automated device, or manual techniques may be used if an automated device is not available. If a manual technique is used, heart rate should be assessed over 1 minute.
- Oxygen saturation should be measured by pulse oximetry with a completely automated device over 1 minute and a representative value recorded.
- Respiratory rate should be assessed over 1 minute.

8.2.8. Clinical Safety Laboratory Assessments – Maternal Participants

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.9. Biological Samples – All Participants

Serum 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.

8.2.10. RSV Vaccine Antibody Testing – All Participants

Sera collected will be assayed for RSV A– and RSV B–neutralizing antibody levels, CCI [redacted]

RSV A– and RSV B–neutralizing antibody levels will be determined and reported as the neutralizing titer. CCI [redacted]

[redacted]

Testing will be performed by a facility designated by Pfizer.

CCI

[redacted]

8.2.13. Blood Volume

8.2.13.1. Maternal Participants: Total Volume of Blood Collected

The total volume of blood collected for antibody assessment over the course of the study will be up to approximately 125 mL depending on when the delivery visit occurs (~25 mL/visit). In addition, sera will be collected at the screening visit for hematology, chemistry, and virology assessments.

8.2.13.2. Infant Participant: Total Volume of Blood Collected

Blood samples will be collected according to the directive 2001/20/EC: Ethical Consideration for Clinical Trials Performed in Children.[27]

Infant participants will be randomly assigned to 1 of 2 blood sampling schedules.

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. If cord blood is unavailable, a venous blood sample may be collected from the infant participant up to 24 hours after birth. The infant's weight must be used to determine the volume of blood that can be collected (see Table 5 below). Venous blood samples will also be collected at approximately 1 and 4 months after birth or 2 and 6 months after birth.

The total volume of venous blood collected from each infant participant for antibody assessment will vary depending on the infant's weight at each visit.

The maximum volume of venous blood to be collected will be no more than 15 mL over the course of 12 months.

Table 5. Guideline for Infant Blood Draw

Body Weight (in kg)	Approximate Volume of Blood (in mL) to Be Collected per Blood Draw
<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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 that 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

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 1 month after the last administration of the investigational product.

In this study, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through 1 month after vaccination. From 1 month after vaccination until the maternal participant completes the study, MAEs and SAEs will be collected.

For the infant participant, the time period for actively eliciting and collecting AEs and SAEs ("active collection period") begins at birth and continues through and including a minimum of 28 days after birth. From Visit 2 until the last study visit, only AEs of special interest, MAEs, and SAEs, including hospitalizations, will be reported.

CCI [redacted]

In addition, AEs occurring up to 48 hours after blood draws CCI [redacted] that are related to study procedures must be reported in the CRF.

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

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

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 of birth, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. In addition, infant deaths after 1 month of age should be reported as SAEs.

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

SAEs occurring in 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 month 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.

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 of birth, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

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 3.

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

8.3.3. Follow-up of AEs and SAEs

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

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

Further information on follow-up procedures is given in Appendix 3.

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.

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):

- 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 investigator site file.

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. 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**.

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

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

8.10. Procedures

8.10.1. Maternal

8.10.1.1. Maternal Participants: Screening (Visit 0) Days -14 to -2 Prior to Vaccination

Maternal participants will be screened from 2 to 14 days prior to administration of the investigational product to confirm that they meet eligibility (all of the inclusion and none of the exclusion) criteria for the study. Maternal participants may be screened 1 day prior to administration of the investigational product if laboratory results are available prior to vaccination.

With the exception of bilirubin, if any Grade 1 hematology or blood chemistry abnormalities are found from samples taken at the screening visit and the investigator believes the results to be erroneous or to represent a stable Grade 1 abnormality, a retest of the abnormal laboratory parameters may be conducted. Maternal participants with stable Grade 1 abnormalities may be considered eligible at the discretion of the investigator.

A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same maternal participant.

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 withdrawn from further participation in the study. All eligible maternal participants will proceed to the vaccination visit.

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- 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, and marijuana usage.
- Obtain and record any medical and obstetric history of clinical significance including history from prior and current pregnancy(ies). Refer to the SRM for further details.
- Record the last menstrual period (LMP) and estimated delivery date (EDD).
- Measure vital signs, including oral temperature, seated blood pressure, and heart rate.
- Measure and record weight and height.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Perform obstetric examination including but not limited to scars from previous deliveries, fundal height, fetal heart tones, and fetal movement.
    - Where an obstetric ultrasound is not performed at ≥18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound and record findings.
- Obtain details of any medications currently taken.
- Obtain details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given at any time during the current pregnancy.
- Obtain details of any vaccinations given at any time during the current pregnancy.

- Obtain blood sample for HBV, HCV, HIV, and syphilis testing.
  - **Note:** Participants testing positive for HIV, or acute or chronic HBV, HCV, or syphilis, will not be eligible for randomization.
- Obtain a blood sample for hematology and blood chemistry assessments.
- Ask the maternal participant to provide a urine sample for glucose and protein testing (urine dipstick).
- Complete the source documents.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- The investigator or an authorized designee completes the CRF.

8.10.1.2. Maternal Participants: Vaccination, Day 1

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

- Review hematology and chemistry laboratory results.
- Review results from HBV, HCV, HIV, and syphilis testing.
- Review all hematology and chemistry results from the previous visit. The hematology and blood chemistry toxicity grading scales[28] should be referenced when assessing a participant's laboratory results. Refer to Section 8.2.8, Section 10.2, and Section 10.3 for details about the reporting of laboratory abnormalities as AEs in the CRF.
- Prior to vaccination, measure vital signs, oral temperature, seated blood pressure, and heart rate.
- Prior to vaccination, measure and record weight.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Ensure that all 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.
- Ask the maternal participant to provide a urine sample for glucose and protein testing (urine dipstick).

- Issue the maternal participant an e-diary and provide instructions on its completion.
- Prior to vaccination, collect a blood sample of approximately 25 mL for serologic assessments.
- Obtain the maternal participant's randomization number and investigational product kit number using the IRT system. Either blinded or unblinded site staff may obtain this information. The infant blood sample schedule will be provided at this time. Refer to the IRT manual for further instructions on this process.
- Unblinded site staff member(s) will administer a single 0.5-mL dose of investigational product into the deltoid muscle of the nondominant arm. Please refer to the IP manual for further instruction on this procedure.
- Blinded site staff must observe the maternal participant for any acute reactions for at least 30 minutes after investigational product administration.
    - **Note:** The first 5 maternal participants vaccinated in the study will be observed for at least 4 hours 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.
- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures, and provide instructions on their use.
- Ask the maternal participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- 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:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site on the nondominant arm measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site on the nondominant arm.
    - Any severe systemic event.
    - Any blackening of the skin (necrosis) at the injection site.
    - Any peeling/scaling of the skin (exfoliative dermatitis).

- Ask the maternal participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind maternal participants that study staff may contact them to obtain additional information on events entered into the e-diary.
- Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Record any medication taken to treat an AE since the last visit.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- Remind the maternal participant to bring the completed e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the 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. Daily review is optimal during the active diary period.

8.10.1.3. Maternal Participants: 2-Week Follow-up Visit (14 to 17 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 maternal participant withdrawal criteria as described in Section 7.2.
- Measure vital signs, including oral temperature, seated blood pressure, and heart rate.
- Measure and record weight.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 25 mL for serologic assessments.
- Review the maternal participant's e-diary data and collect the e-diary (if applicable). 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 antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record any medication taken to treat an AE since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Ask the maternal participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.1.4. Maternal Participants: 1-Month Follow-up Visit (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.
- Measure vital signs, including oral temperature, seated blood pressure, and heart rate.
- Measure and record weight.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 25 mL for serologic assessments.
- Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record any medication taken to treat an AE since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Complete the maternal participant's source documents.
- Ask the maternal participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Record AEs as described in Section 8.3 and Section 10.3.3.
- The investigator or an authorized designee completes the CRF.

8.10.1.5. Maternal Participants: Delivery

- 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.
- Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record any medication as described in Section 6.5.3.
- Record details of any nonstudy vaccinations given since the last visit.
- Collect a blood sample of approximately 25 mL for serologic assessments. Refer to the SRM for blood sample collection guidelines.
- Record pregnancy outcome information including vital status of the infant (live, stillbirth).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor’s visit, emergency room visit) or hospitalization occurs.
- Ask the maternal participant to contact the site staff or investigator if her newborn infant meets the acute illness visit criteria.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- Complete the participant’s source documents.
- The investigator or an authorized designee completes the CRF.

8.10.1.6. Maternal Participants: 1-Month-Postdelivery Follow-up (28 to 35 Days After Delivery)

- Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record any medication as described in Section 6.5.3.
- Record details of any nonstudy vaccinations given since the last visit.
- Record AEs as described in Section 8.3 and Section 10.3.3.

- Complete the maternal participant's source documents.
- Ask the maternal participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the maternal participant to contact the site staff or investigator if her infant meets the acute illness visit criteria.
- The investigator or an authorized designee completes the CRF.

8.10.1.7. Maternal Participants: 6-Month-Postdelivery Visit (168 to 210 Days After Delivery)

- Collect a blood sample of approximately 25 mL for serologic assessments. Refer to the SRM for blood sample collection guidelines.
- Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Record any medication as described in Section 6.5.3.
- Ask the maternal participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the maternal participant to contact the site staff or investigator if her infant meets the acute illness visit criteria.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- Complete the maternal participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.1.8. Maternal Participants: 12-Month-Postdelivery Follow-up (350-378 Days After Delivery)

- Record details of any antenatal steroid treatment, monoclonal antibodies, blood transfusions (eg, whole blood, packed cells), or Rho(D) immune globulin (eg, RhoGam) given since the last visit.
- Record details of any nonstudy vaccinations given since the last visit.
- Record any medication as described in Section 6.5.3.

- Record AEs as described in Section 8.3 and Section 10.3.3.
- Complete the maternal participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.1.9. Maternal Participants: 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 visit is required.

- redness at the injection site measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site measuring >20 measuring device units (>10.0 cm),
- severe injection site pain,
- fever ≥102.1°F (≥39.0°C),
- severe fatigue,
- severe headache,
- severe nausea,
- severe vomiting,
- severe diarrhea,
- severe muscle pain,
- severe joint pain.
- any necrosis at the injection site,
- any exfoliative dermatitis.

A site visit 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 maternal participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or

- The investigator determines that the visit is not required.

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

If the maternal participant is unable to attend the unscheduled visit, 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, who will:

- Measure oral temperature.
- Measure the maternal participant's heart rate.
- Measure the maternal participant's blood pressure (seated).
- Measure the minimum and maximum diameters of redness (if present).
- Measure the minimum and maximum diameters of swelling (if present).
- Assess any necrosis at the injection site.
- Assess any exfoliative dermatitis.
- Assess any injection site pain that is present in accordance with the reactogenicity grading scale provided in Section 8.2.2.
- Assess for lymphadenopathy associated with any local reaction.
- 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 8.2.3.
- Ask the maternal participant if she attended an emergency room visit or was hospitalized.
- For severe pain at the injection site associated with an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, or any necrosis or exfoliative dermatitis, the investigator must assess these events in accordance with the Assessment of Intensity grading scale provided in Section 10.3.3 for documentation on the AE CRF.
- Record any medication as described in Section 6.5.3.
- Record AEs as described in Section 8.3 and Section 10.3.3.

- Complete the source documents.
- The investigator or an authorized designee will complete the CRFs.

Maternal participants will be instructed to contact the site to report any significant illness, medically attended event, or hospitalization that occurs during the study period. Study staff may contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

8.10.2. Infant

8.10.2.1. Infant Participants: Visit 1 – Birth (Birth to 7 Days After Birth)

- Assign a single infant participant identifier using the IRT system (or equivalent).
- Ensure a cord blood sample of up to approximately 10 mL was collected. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord 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 venous blood sample may be collected in the infant participants up to 24 hours after birth. The volume of blood collected will be based on the weight of the infant (refer to Table 5).
- Ensure and document that all of 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 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 gestational age, Apgar score, and Ballard 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.
- Perform physical examination, if not performed as part of routine care, evaluating 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 and AE pages of the CRF.

    - Record details of any congenital abnormality.

- Record nonstudy vaccine information.

- Record monoclonal antibodies (eg, Synagis) or blood transfusions (eg, whole blood, packed cells) given since birth.

- Record any medication as described in Section 6.5.5.

- Record AEs as described in Section 8.3 and Section 10.3.3.

- 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 acute illness visit criteria.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

8.10.2.2. Infant Participants: Visit 2 – 1-Month Follow-up (28 to 35 Days After Birth)

- Measure vital signs, including rectal temperature, heart rate, and respiratory rate.

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

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

- Perform physical examination, if not performed as part of routine care, evaluating 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. 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.

    - Obtain and record details of any newly emergent congenital medical history.

- Obtain and record details of any vaccinations, monoclonal antibodies (eg, Synagis), or blood transfusions (eg, whole blood, packed cells) given since the last visit.

- For infants randomly assigned to the Visit 2 (1-month follow-up) and Visit 4 (4-month follow-up) sampling schedule, collect a blood sample of up to 5.0 mL for serologic assessments based on the infant's weight (refer to Table 5).

- Record any medication as described in Section 6.5.5.Record AEs as described in Section 8.3 and Section 10.3.3.

- 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 acute illness visit criteria.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.2.3. Infant Participants: Visit 3 – 2-Month Follow-up (49 to 63 Days After Birth)

- Measure vital signs, including rectal temperature, heart rate, and respiratory rate.
- Obtain and record the infant's length, head circumference, and weight.
- Obtain and record background factors as described in Section 10.5.
- Perform physical examination, if not performed as part of routine care, evaluating 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. 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.
    - Obtain and record details of any newly emergent congenital medical history.
- Obtain and record details of any vaccinations, monoclonal antibodies (eg, Synagis), or blood transfusions (eg, whole blood, packed cells) given since the last visit.
- For infants randomly assigned to the Visit 3 (2-month follow-up) and Visit 5 (6-month follow-up) sampling schedule, collect a blood sample of up to 5.0 mL for serologic assessments based on the infant's weight (refer to Table 5).
- Record any medication as described in Section 6.5.5.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- 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 acute illness visit criteria.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.2.4. Infant Participants: Visit 4 – 4-Month Follow-up (112 to 126 Days After Birth)

- Measure vital signs, including rectal temperature, heart rate, and respiratory rate.
- Obtain and record the infant's length, head circumference, and weight.
- Obtain and record background factors as described in Section 10.5.
- Perform physical examination, if not performed as part of routine care, evaluating 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. 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.
    - Obtain and record details of any newly emergent congenital medical history.
- Obtain and record details of any vaccinations, monoclonal antibodies (eg, Synagis), or blood transfusions (eg, whole blood, packed cells) given since the last visit.
- For infants randomly assigned to the Visit 2 (1-month follow-up) and Visit 4 (4-month follow-up) sampling schedule, collect a blood sample of up to 5.0 mL for serologic assessments based on the infant's weight (refer to Table 5).
- Record any medication as described in Section 6.5.5.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- 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 acute illness visit criteria.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.2.5. Infant Participants: Visit 5 – 6-Month Follow-up (168 to 210 Days After Birth)

- Measure vital signs, including rectal temperature, heart rate, and respiratory rate.
- Obtain and record the infant's length, head circumference, and weight.
- Obtain and record background factors as described in Section 10.5.
- Perform physical examination, if not performed as part of routine care, evaluating 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. 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.

    - Obtain and record details of any newly emergent congenital medical history.

- Obtain and record details of any vaccinations, monoclonal antibodies (eg, Synagis), or blood transfusions (eg, whole blood, packed cells) given since the last visit.

- For infants randomly assigned to the Visit 3 (2-month follow-up) and Visit 5 (6-month follow-up) sampling schedule, collect a blood sample of up to 5.0 mL for serologic assessments based on the infant's weight (refer to Table 5).

- Record any medication as described in Section 6.5.5.

- Record AEs as described in Section 8.3 and Section 10.3.3.

- 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 acute illness visit criteria.

- Complete the infant participant's source documents.

- The investigator or an authorized designee completes the CRF.

8.10.2.6. Infant Participants: Visit 6 – 12-Month Follow-up (350 to 378 Days After Birth)

- Measure vital signs, including rectal temperature, heart rate, and respiratory rate.

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

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

- Perform physical examination, if not performed as part of routine care, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; back; abdomen; musculoskeletal; extremities; genitourinary; neurological; and lymph nodes. 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.

    - Obtain and record details of any newly emergent congenital medical history.

- Obtain and record details of any vaccinations, monoclonal antibodies (eg, Synagis), or blood transfusions (eg, whole blood, packed cells) given since the last visit.
- Record any medication as described in Section 6.5.5.
- Record AEs as described in Section 8.3 and Section 10.3.3.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

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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

There is no statistical hypothesis specified in this study. The primary objectives are to describe the safety and tolerability of an RSV vaccine on maternal participants and to assess the safety of maternal immunization in infant participants born to women 18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy. The safety population will be used to evaluate the primary objectives.

9.1.1. Estimands – Maternal Participants

9.1.1.1. Safety:

In maternal participants receiving 1 dose of investigational product:

- The percentage of maternal participants reporting local reactions
- The percentage of maternal participants reporting systemic events
- The percentage of maternal participants reporting AEs

- The percentage of maternal participants reporting obstetric complications, MAEs, and SAEs

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

9.1.1.2. 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–neutralizing antibody titers
- The immune response, estimated by the GMFR from baseline in RSV A– and RSV B–neutralizing antibody titers
- GMR, estimated by the ratio of the GMTs for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group and 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 violation observations will be censored.

9.1.2. Estimands – Infant Participants

9.1.2.1. 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
- The percentage of infant participants having SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs

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

9.1.2.2. 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

- GMR, estimated by the ratio of the GMTs for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group and 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 MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or violation observations will be censored.

9.2. Sample Size Determination

This is a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study to assess the safety, tolerability, and immunogenicity of 2 dose levels of the RSV vaccine candidate with or without $Al(OH)_3$ in pregnant women ≥18 through ≤49 years of age and to assess the safety and characteristics of transplacentally transferred antibodies, CCI [redacted] The sample size for this study is not driven by any specific hypothesis testing.

Up to 650 maternal participants will be randomized in a 1:1:1:1:1 ratio to receive a single dose of one of the 4 RSV vaccine dose/formulations or placebo.

Table 6 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes based on anticipated northern hemisphere enrollment. For example, if the true AE rate is 1%, with 100 participants in a group, there is 63% probability of observing at least 1 AE.

Table 6. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Sample Size (N)	Assumed True Event Rate of an AE						
	0.5%	**1%**	**2%**	**3%**	**4%**	**5%**	**10%**
100	0.39	0.63	0.87	0.95	0.98	>0.99	>0.99
200	0.63	0.87	0.98	>0.99	>0.99	>0.99	>0.99
400	0.87	0.98	>0.99	>0.99	>0.99	>0.99	>0.99

Note: A total of 100 maternal participants are to be vaccinated with each dose/formulation of RSV vaccine; 200 maternal participants are to be vaccinated with each dose level of RSV vaccine (120 µg or 240 µg) and each formulation of RSV vaccine (with or without $Al[OH]_3$); and 400 maternal participants are to be vaccinated with any dose/formulation of RSV vaccine.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined for maternal and infant 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 - 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.
Evaluable - 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.
Modified intent-to-treat (mITT) - Maternal	All randomized maternal participants who receive investigational product and have at least 1 valid and determinate assay result for the proposed analysis.
mITT - Infant	All infant participants who are born to vaccinated maternal participants and have at least 1 valid and determinate assay result for the proposed analysis.
Safety - Maternal	All randomized maternal participants who receive investigational product.
Safety - Infant	All infant participants who are born to vaccinated maternal participants.

9.4. Statistical Analyses

The SAP will be developed and finalized before the database lock of the first planned analysis. It 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 and secondary endpoints.

9.4.1. Immunogenicity CCI [redacted] Analyses

Endpoint	Statistical Analysis Methods
Secondary	• For maternal participants and for infant participants, GMTs of the RSV A– and RSV B–neutralizing antibody titers at each available time point will be descriptively summarized for each vaccine group, along with associated 2-sided 95% confidence intervals (CIs). The GMT will be calculated as the mean of the antibody titers after the logarithm transformation and then transformed back to its original scale. Two (2)-sided 95% CIs will be constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed based on Student's t distribution. • For maternal participants, GMFRs and associated 2-sided 95% CIs will be provided for RSV A– and RSV B–neutralizing antibody titers from before vaccination to each available time point after vaccination for each vaccine group. The GMFR will be calculated as the mean of the difference of logarithmically transformed antibody titers (postvaccination minus prevaccination for each participant) and transformed back to the original units. Two (2)-sided 95% CIs will be computed by back transformation of the

Endpoint	Statistical Analysis Methods
	CIs using 1-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results. • For maternal participants and for infant participants, GMRs of the RSV vaccine group to the placebo group for the RSV A– and RSV B–neutralizing antibody titers at each available time point after vaccination will be calculated, along with associated 2-sided 95% CIs. The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and transformed back to the original units. Two (2)-sided 95% CIs will also be computed by back transformation of the CIs using 2-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results. Titers below the lower limit of quantitation (LLOQ) or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ for analysis. The above analyses are based on the evaluable population. An additional analysis will be performed based on the mITT population if there is enough difference between the mITT population and the evaluable population. Participants will be summarized according to the vaccine group to which they (for maternal participants) or their mothers (for infant participants) were randomized. Missing serology data will not be imputed.

[redacted]

9.4.1.1. Analysis of Immunogenicity Endpoints

Immunogenicity endpoints are secondary [redacted] in the study as listed in Section 3. The analyses of immunogenicity endpoints will be based on the evaluable populations. An additional analysis will be performed based on mITT populations if there is enough difference between 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 [redacted] 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).
- 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).
- 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).

CCI [redacted]

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.

Subgroup analyses of the secondary CCI [redacted] immunogenicity endpoints will be performed, including an analysis based on gestational-age-at-the-time-of-vaccination 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.

CCI [redacted]

9.4.2. Safety Analyses

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 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 percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. There is no preidentified Tier 1 event for this study. A Medical Dictionary for Regulatory Activities (MedDRA) preferred term is defined as a Tier 2 event if there are 4 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	• Not applicable (N/A)
CCI [redacted]	[redacted]

9.4.2.1. Analysis of the Primary Safety Endpoints

The safety endpoints are primary in the study and their analyses are based on the safety populations. Safety data will be analyzed separately for maternal participants and infants participants. Maternal participants will be analyzed according to the investigational product received, and infant participants will be analyzed according to the investigational product their mothers (maternal participants) received.

The safety analyses for maternal participants are descriptive evaluations of local reactions, systemic events, AEs, obstetric complications, MAEs, and SAEs. Obstetric complication will be defined and identified by the Pfizer study clinician prior to study unblinding. The safety analyses for infant participants are descriptive evaluations of birth outcomes, AEs, SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs. AEs and SAEs will be categorized according to MedDRA terms. The number and percentage of participants reporting each event and 2-sided 95% exact CIs will be provided by vaccine group.

9.5. Interim Analyses

No formal interim analysis is planned for this study.

9.5.1. Analysis Timing

The timings of the planned analyses prior to the final analysis are described below.

5. An analysis will be performed when the delivery-visit RSV-neutralizing antibody titer data from all maternal and infant participants and the 1-month-after-birth visit data for infant participants are available.

6. A further analysis will be performed when all data are available from the infant participants' 6-month visits.

Additional analyses may be conducted at any time to support internal program-level decisions as needed. These analyses may be based on fewer than the total planned number of participants.

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

9.5.2. Data Monitoring Committee

This study will use an IRC and an E-DMC. Refer to the IRC and E-DMC charters 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 (with the exception of the unblinded clinician who is independent of the study team) 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.

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) Good Clinical Practice (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 of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants or their legally acceptable representative 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 or his or her legally acceptable representative 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 or their legally acceptable representative 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 or his or her legally acceptable representative 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 or their legally acceptable representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally acceptable representative.

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.

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 standard operating procedures (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 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.

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.

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 electronic CRF (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.

10.1.9. 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: Clinical Laboratory Tests

Investigators must document their review of each laboratory safety report.

10.2.1. HIV, Hepatitis B Surface Antigen (HBsAg), Hepatitis C, and Syphilis Serology Testing

At the screening visit (Visit 0, all maternal participants), approximately 10 mL of blood will be drawn to determine the maternal participant's HIV status and rule out infection with HBV, HCV, or syphilis. The results from these tests will be available and reviewed at the vaccination visit.

10.2.2. Hematology and Blood Chemistry

Blood samples for hematology and blood chemistry assessments (approximately 10 mL) will be collected for all maternal participants at screening (Visit 0).

Repeat testing of the protocol-required laboratory parameters is permitted to confirm results. Additional laboratory testing not specified in the protocol may be performed at the discretion of the investigator as follow-up to an AE and should be recorded in the maternal participant's source documents. The safety laboratory tests in Table 7 will be performed at times defined in the SoA.

Table 7. Laboratory Tests

Hematology	Chemistry
Hemoglobin	BUN and creatinine
Hematocrit	AST, ALT
RBC count	Total bilirubin
Platelet count	Alkaline phosphatase
WBC count	
Total neutrophils (Abs)	
Eosinophils (Abs)	
Monocytes (Abs)	
Basophils (Abs)	
Lymphocytes (Abs)	

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell.

A toxicity grading scale adapted for use in pregnant women will be used to grade laboratory test abnormalities.[28]

If abnormal laboratory parameters are reported at screening (Visit 0) and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested.

10.3. Appendix 3: 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.

10.3.1. 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, 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. • 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.

10.3.1.1. Definition of MAE

An MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (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.

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.
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 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.

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via 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.

10.4. Appendix 4: 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).

- 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.

10.5. Appendix 5: Background Factors

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

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

Information on the following will be collected at each postbirth visit, [redacted]

- Childcare framework (for infant participant)
- Breastfeeding information

10.6. Appendix 6: Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
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
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
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
eCRF	electronic CRF
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
FIH	first-in-human
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator’s brochure
ICD	informed consent document

Abbreviation	Term
ICH	International Council for Harmonisation
ID	identification
CCI [redacted]	[redacted]
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
IV	intravenous
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LMIC	lower- and middle-income country
LMP	last menstrual period
CCI [redacted]	[redacted]
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NaCL	sodium chloride
PCD	primary completion date
CCI [redacted]	[redacted]
POC	proof-of-concept
PT	prothrombin time
RBC	red blood cell
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
CCI [redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
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
CCI [redacted]	[redacted]
US	United States
WBC	white blood cell

10.7. Appendix 7: Country-Specific Appendix – Applicable to Argentina Only

The inclusion criterion below replaces Criterion 1 in the original protocol because of the board of health request for the upper age limit for maternal participants to be 39 years:

Section 5.1.1 Inclusion Criteria – Maternal Participants

Age and Sex:

1. Healthy women ≥18 and ≤39 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, and whose fetus has no significant abnormalities observed on ultrasound.

   Note: Gestational age must be based upon ultrasound results obtained at ≥18 weeks of pregnancy.

11. REFERENCES

1. Meissner HC. Respiratory syncytial virus. In: Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases*. 5th ed. Philadelphia, PA: Elsevier; 2018:1162-1165. (Available upon request).

2. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet.* 2017;390(10098):946-958.

3. Scheltema NM, Gentile A, Lucion F, et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. *Lancet Glob Health*. 2017;5(10):e984-e991.

4. Parikh RC, McLaurin KK, Margulis AV, et al. Chronologic age at hospitalization for respiratory syncytial virus among preterm and term infants in the United States. *Infect Dis Ther*. 2017;6(4):477-486.

5. American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Policy statement—updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2):415-420.

6. Blanken MO, Rovers MM, Molenaar JM, et al; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013;368(19):1791-1799.

7. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541-545. (Available upon request).

8. Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Trop Med Int Health*. 1998;3(4):268-280.

9. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child*. 1986;140(6):543-546.

10. American Academy of Pediatrics. Respiratory Syncytial Virus. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: AAP; 2018:682-92. (Available upon request).

11. Prescott WA Jr, Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. *Pharmacoeconomics*. 2010;28(4):279-293.

12. Full Prescribing Information for Synagis. https://www.azpicentral.com/synagis/synagis.pdf#page=1. Accessed 15 Nov 2018.

13 Munoz FM, Ralston SL, Meissner HC. RSV recommendations unchanged after review of new data. *AAP News*. 19 Oct 2017. http://www.aappublications.org/news/2017/10/19/RSV101917. Accessed 15 Nov 2018.

14 The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102(3):531-537.

15 Baker CJ, Carey VJ, Rench MA, et al. Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. *J Infect Dis*. 2014;209(5):781-788.

16 Dangor Z, Kwatra G, Izu A, et al. Correlates of protection of serotype-specific capsular antibody and invasive Group B *Streptococcus* disease in South African infants. *Vaccine*. 2015;33(48):6793-6799.

17 Skoff TH, Blain AE, Watt J, et al. The impact of the U.S. maternal Tdap vaccination program on preventing pertussis in infants <2 months of age: a case-control evaluation. *Clin Infect Dis*. 2017;65(12):1977-1983.

18 Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of vaccination during pregnancy to prevent infant pertussis. *Pediatrics*. 2017;139(5):e20164091.

19 Madhi SA, Cutland CL, Kuwanda L, et al; Maternal Flu Trial (MatFlu) Team. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med*. 2014;371(10):918-931.

20 Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vazquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis*. 2010;51(12):1355-1361.

21 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-e348.

22 McLellan JS, Chen M, Leung S, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. *Science*. 2013;340(6136):1113-1117.

23 Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am J Epidemiol*. 1969;89(4):422-434.

24 Graham BS. Biological challenges and technological opportunities for respiratory syncytial virus vaccine development. *Immunol Rev*. 2011;239(1):149-166.

25 Munoz FM, Piedra PA, Glezen WP. Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women. *Vaccine*. 2003;21(24):3465-3467.

26. World Health Organization. Congenital anomalies. http://www.who.int/topics/congenital_anomalies/en/. Accessed 08 May 2018.

27. European Commission. Ethical considerations for clinical trials on medicinal products conducted with minors. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf. Accessed 21 February 2019.

28. Sheffield JS, Munoz FM, Beigi RH, et al. Research on vaccines during pregnancy: reference values for vital signs and laboratory assessments. *Vaccine*. 2013;31(40):4264-4273.

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