



**A PHASE 3, RANDOMIZED, DOUBLE-BLINDED,
PLACEBO-CONTROLLED TRIAL TO EVALUATE THE SAFETY,
TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL
VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN PREGNANT
PARTICIPANTS LIVING WITH HIV AND THEIR INFANTS**

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Study Intervention Name:	Respiratory Syncytial Virus (RSV) Vaccine
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EudraCT Number:	N/A
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3671032
Phase:	3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001, USA

Brief Title:

A Phase 3 Trial to Evaluate the Safety, Tolerability, and Immunogenicity of RSVpreF in Pregnant Participants Living With HIV and Their Infants

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1. PROTOCOL SUMMARY

1.1. Synopsis

This is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study in which pregnant participants ≤ 49 years of age living with HIV will receive 1 dose of RSVpreF or placebo. Approximately 330 pregnant participants living with HIV will be assigned to either the RSVpreF or placebo group. 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.

Protocol Title:

A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Pregnant Participants Living With HIV and Their Infants

Brief Title: A Phase 3 Trial to Evaluate the Safety, Tolerability, and Immunogenicity of RSVpreF in Pregnant Participants Living With HIV and Their Infants

Regulatory Agency Identification Number(s):

US IND Number:	017931
EudraCT/EU CT Number:	N/A
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3671032
Phase:	3

Rationale:

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract illness (LRTI) among infants and young children globally. Despite morbidity and mortality, there is currently no treatment for RSV in children.

Pfizer is developing a vaccine to protect against RSV disease. The vaccine, RSV stabilized prefusion F subunit vaccine (RSVpreF), contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. Studies of RSVpreF in both the older adult (C3671013) and maternal (C3671008) populations met primary efficacy endpoints, and in both populations the vaccine has been shown to be well tolerated, with no safety concerns. On 31 May 2023, based on efficacy and safety data from the older adult population study (C3671013), the Food and Drug Administration (FDA) approved RSVpreF (Abrysvo™) for marketing in individuals 60 years of age and older in the United States.

Given that infants born to mothers living with human immunodeficiency virus (HIV) are at significant risk of morbidity and mortality due to RSV infection, it is important that the safety and immune response of RSVpreF be evaluated in this population.

Objectives, Endpoints, and Estimands:

Maternal Participants

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To describe the safety profile of RSVpreF in maternal participants living with HIV	- Prespecified local reactions (pain at the injection site, redness, and swelling) - Prespecified systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) - AEs - AESIs - SAEs	In maternal participants living with HIV receiving 1 dose of the study intervention, the proportion of the following safety events reported: - 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 - AESIs throughout the study - SAEs throughout the study
Secondary:	Secondary:	Secondary:
To describe the immune responses elicited by RSVpreF in maternal participants living with HIV	RSV A and RSV B serum NTs	In maternal participants in compliance with the key protocol criteria (evaluable immunogenicity population): - GMT of the NTs for RSV A and RSV B at each blood sampling visit - GMFR of the NTs for RSV A and RSV B from before vaccination to the postvaccination blood sampling visit
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To descriptively compare the immune responses elicited by RSVpreF between pregnant participants living with HIV from this study and pregnant participants without HIV from Study C3671008	RSV A and RSV B serum NTs	

Infant Participants

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To describe the safety profile of RSVpreF	- Specific birth outcomes - AEs from birth through 1 month of age - SAEs and NDCMCs from birth through 6 months of age	In infant participants born to maternal participants living with HIV receiving 1 dose of the study intervention, the percentage of participants with each safety endpoint
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To evaluate RSV serum NTs elicited by RSVpreF and transferred transplacentally	RSV A and RSV B serum NTs measured at birth	

Overall Design:

This is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of Pfizer’s RSVpreF administered to pregnant participants living with HIV, as well as safety and immunogenicity in their infants.

Study-eligible, pregnant participants living with HIV providing informed consent will be referred to as “maternal participants” and will receive a single dose of RSVpreF or placebo (1:1 randomization). Follow-up for maternal participants will continue through pregnancy and until 6 months after delivery. Assessments will include evaluations of safety, tolerability, and immunogenicity of the vaccine in maternal participants.

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

To assess immunogenicity, all maternal participants will have blood drawn at baseline, prior to vaccination, and at delivery. Immune responses elicited by RSVpreF in maternal participants in this study will be analyzed and will also be compared to immune responses elicited by RSVpreF in maternal participants in the C3671008 study, in which RSVpreF efficacy was demonstrated.

Local reaction and systemic event data will be collected in an electronic diary (e-diary) during the 7-day follow-up period, or longer, for ongoing events after study vaccination (ie, from Day 1, the day of vaccination, until event resolution). After e-diary collection, the site will follow-up with the participant for any ongoing events. Reported Grade 3 and potentially Grade 4 reactogenicity events will be assessed by the investigator or a qualified designee to determine unscheduled medical visit requirements.

For all maternal participants, adverse events (AEs) will be collected from informed consent through 1 month following study intervention administration. Adverse events of special interest (AESIs) and serious adverse events (SAEs) will be collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected.

Infants born to participants who receive the study intervention will be referred to as “infant participants.” Infant participants will be followed until 6 months after birth. AEs will be collected from birth through 1 month following birth, and newly diagnosed chronic medical conditions (NDCMCs) and SAEs will be collected from birth throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected.

Number of Participants:

It is anticipated that approximately 330 maternal participants will be randomized in the study.

Study Population:

Inclusion Criteria - Maternal Participants

Participants must meet the following **key** inclusion criteria to be eligible for enrollment into the study.

- Women ≤ 49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated **singleton pregnancy** who are at no known increased risk for complications.
- Confirmed stable HIV disease, defined as a documented HIV viral load < 1000 copies/mL and CD4 count > 200 cells/mm³, within 14 days of randomization.
- Current and stable use of antiretroviral therapy (ART) for at least 90 days prior to enrollment.
- Had a fetal anomaly ultrasound examination performed at ≥ 18 weeks of pregnancy with no significant fetal abnormalities observed.
- Intention to deliver at a hospital or birthing facility where study procedures can be obtained.
- Participant is willing to give informed consent for the participant’s infant to participate in the study.
- Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion Criteria - Maternal Participants

Participants with any of the following **key** characteristics/conditions will be excluded:

- Prepregnancy body mass index (BMI) of $>40 \text{ kg/m}^2$. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used.
- Participant with opportunistic infections or malignancy.
- History of active chronic viral hepatitis with biochemical evidence of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >5 times the upper limit of normal within 6 months before enrollment.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention or any related vaccine.
- Current pregnancy resulting from in vitro fertilization. Participants known to have used clomiphene citrate and/or letrozole with or without intrauterine insemination (IUI) are permitted.
- Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:
 - Preeclampsia, eclampsia, or uncontrolled gestational hypertension.
 - Placental abnormality.
 - Polyhydramnios or oligohydramnios.
 - Significant bleeding or blood clotting disorder.
 - Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism. This also includes disorders of glucose intolerance (eg, diabetes mellitus type 1 or 2) antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent.
 - Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth.
- Prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:

- Prior preterm delivery at ≤ 34 weeks' gestation
- Prior stillbirth or neonatal death
- Previous infant with a known genetic disorder or significant congenital anomaly
- Non-HIV-associated congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications.
- Antituberculosis treatment use currently or at any time during this current pregnancy.

Inclusion Criteria - Infant Participants

- Evidence of a signed and dated ICD, signed by the parent(s)/legal guardian(s).

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

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

Exclusion Criteria - Infant Participants

- Infant who is a direct descendant (eg, child or grandchild) of the investigator site staff or sponsor and sponsor delegate employees directly involved in the conduct of the study.

Study Arms and Duration:

Study Arms:

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

Study Duration:

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

All infants will participate from the time of birth and for at least 6 months after birth.

Statistical Methods:

The statistical analysis plan (SAP) will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data.

A summary of the planned statistical analyses of the primary and secondary endpoints can be found in the protocol.

This study is descriptive in nature, and therefore the planned sample size for the study is not based on any statistical hypothesis testing.

The primary maternal participant safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/AESIs/SAEs for each vaccine group. The primary infant participant safety objective will be evaluated by descriptive summary statistics for AEs/SAEs for each maternal vaccine group. A 3-tier approach will be used to summarize AEs in the study.

The secondary maternal (immunogenicity) objective will be evaluated descriptively by geometric mean titer (GMT), geometric mean fold rise (GMFR), and the associated 95% confidence intervals (CIs) for neutralizing titers (NTs) at the various time points.

Immune response to RSVpreF will be compared between pregnant participants in this study living with HIV and pregnant participants without HIV from Study C3671008, based on the ratio of GMTs using a 2-fold noninferiority margin.

Ethical Considerations:

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF support a favorable benefit/risk profile and support the clinical development of the vaccine. Considering the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to participants in this study.

RSVpreF is an F glycoprotein subunit stabilized in the prefusion conformation, eliciting strong neutralizing antibodies as established in the adult studies, and has already shown efficacy in preventing LRTI in older adults and severe LRTI in infants born to vaccinated healthy mothers without HIV.

Based on the experience with RSVpreF, the potential risks are:

- Local reactions, such as injection site redness, injection site swelling, and injection site pain; systemic events, such as fatigue, headache, muscle pain, and joint pain; and fever.

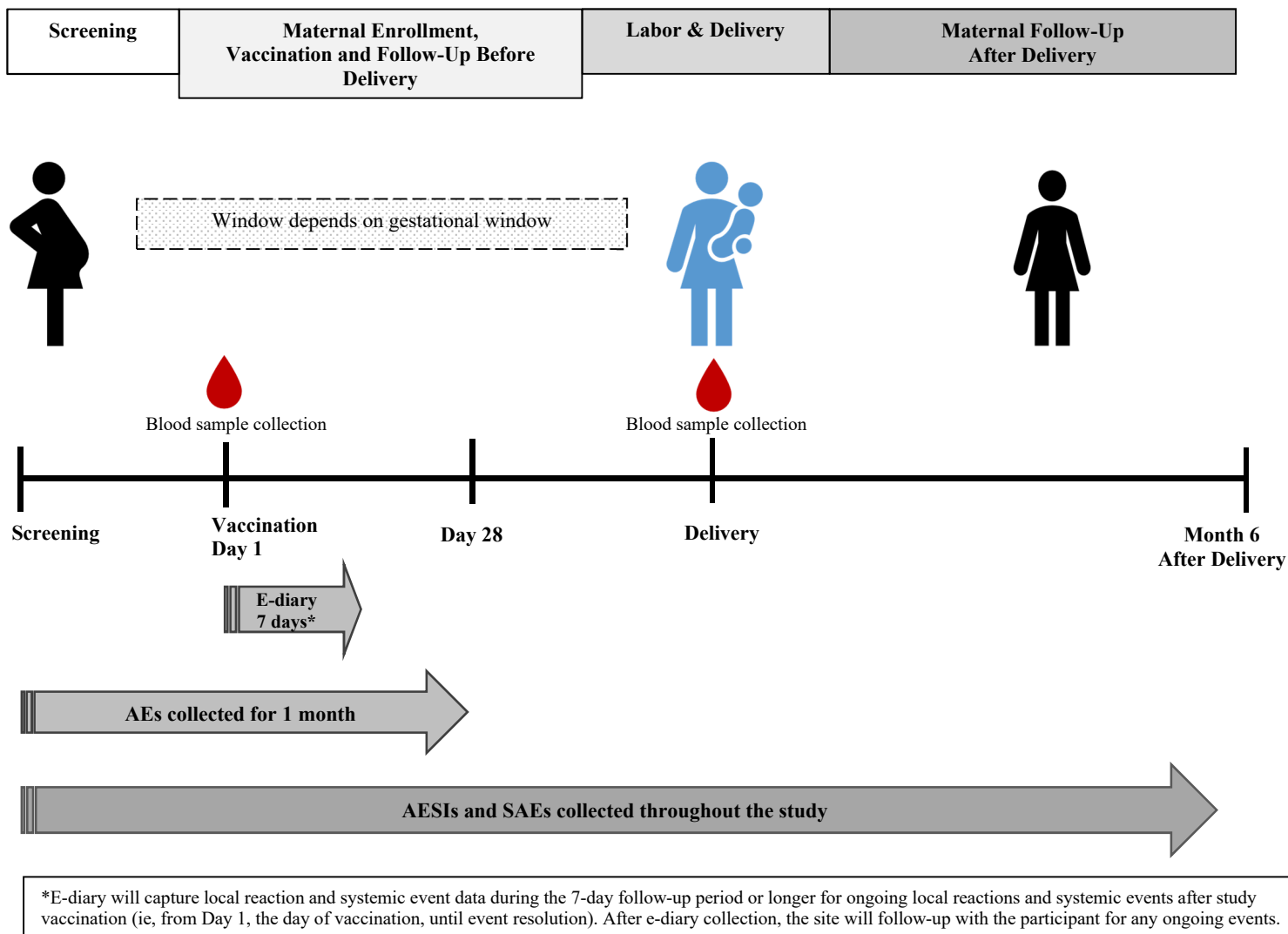
- One case of Guillain-Barre syndrome and 1 case of Miller Fisher syndrome with a plausible temporal relationship with vaccination were identified in Study C3671013, conducted in participants 60 years of age and older.
- Safety profile of a novel vaccine is not yet fully characterized.

The study procedure–related risks include:

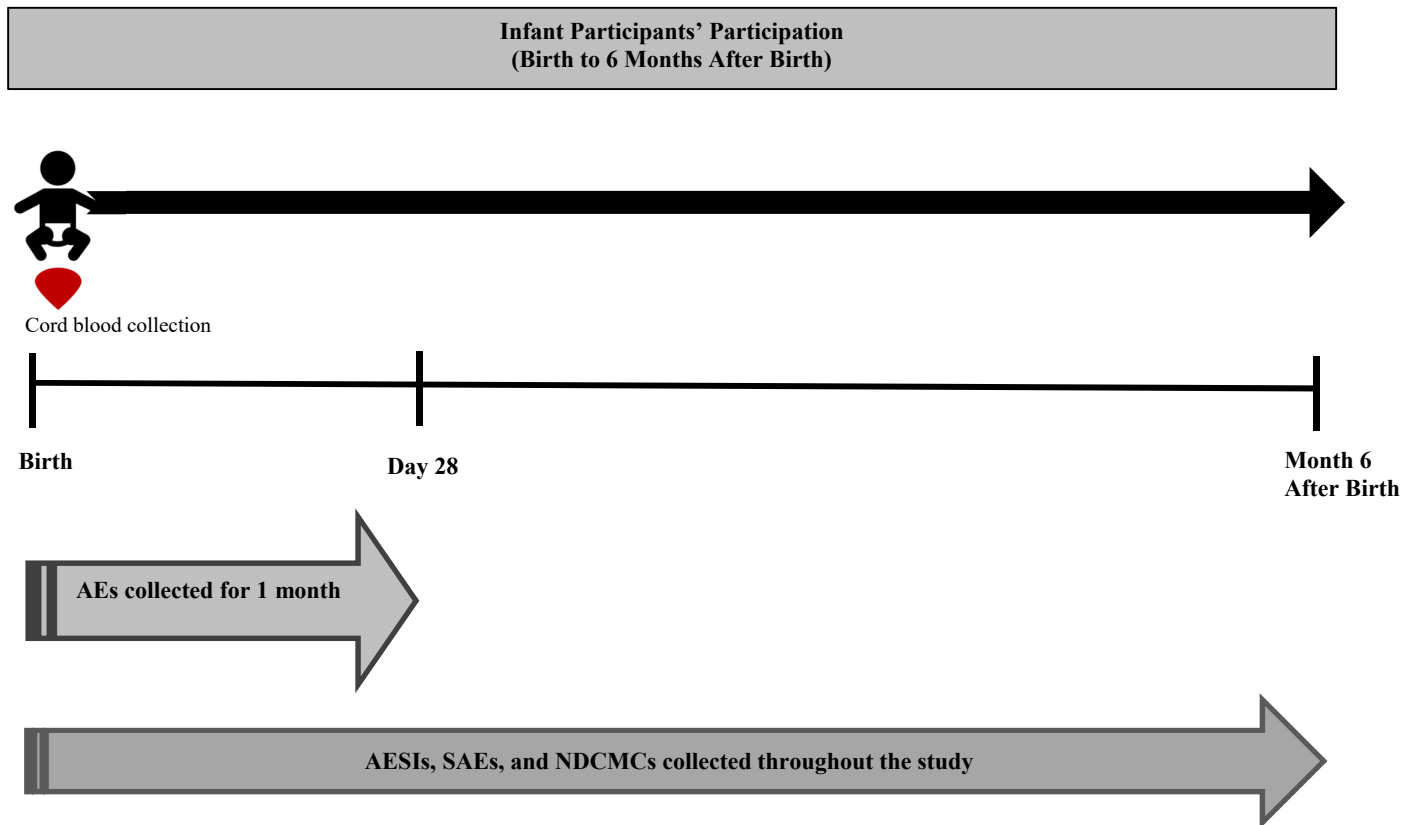
- Venipuncture will be performed during the study.

1.2. Schematic for Study Participants

1.2.1. Study Design – Maternal Participants



1.2.2. Study Design – Infant Participants



1.3. Schedule of Activities

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

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

1.3.1. Schedule of Activities for Maternal Participants

Visit Description	Screening ^a	Vaccination Visit	1-Month Follow-Up ^b	Delivery ^c	6-Month Postdelivery
Visit Window (Days)		Vaccination Day 1	28 to 42 Days After Vaccination	Delivery	180 to 210 Days After Delivery
Type of Visit	Clinic	Clinic	Clinic, Home, or Telephone	Maternity Unit	Clinic, Home, or Telephone
Informed consent for maternal participant and the participant's infant	X				
Assign single maternal participant identifier	X				
Demography	X				
Medical history, including obstetric history	X				
Obstetric ultrasound examination at ≥ 18 weeks (if needed) ^d	X	X			
Record standard-of-care syphilis, HBV, and active TB screening results (if available)	X				
Record standard-of-care CD4 count and HIV viral load results (if available)	X	X	X	X	X
If appropriate results are not available as standard of care, collect sample(s) for syphilis, HBV, and active TB screening, and CD4 count and HIV viral load assessment ^e	X				
Record current/former alcohol, tobacco, marijuana, or any illicit drug usage	X				

Visit Description	Screening ^a	Vaccination Visit	1-Month Follow-Up ^b	Delivery ^c	6-Month Postdelivery
Visit Window (Days)		Vaccination Day 1	28 to 42 Days After Vaccination	Delivery	180 to 210 Days After Delivery
Type of Visit	Clinic	Clinic	Clinic, Home, or Telephone	Maternity Unit	Clinic, Home, or Telephone
Record nonstudy vaccine information and antiretroviral medications	X	X	X	X	X
Record details of any antenatal and/or postnatal steroid treatment, monoclonal antibodies, blood products, or Rho(D) immune globulin	X	X	X	X	X
Targeted physical and obstetric examination performed on the same day or within 7 days before the vaccination visit		X			
Record vital signs (body temperature, seated blood pressure, and heart rate)		X			
Review eligibility criteria	X	X	X	X	
Review temporary delay criteria		X			
Prevaccination blood draw for serologic assessment (~15 mL) on the same day or within 7 days before the vaccination visit		X			
Assign randomization and container number		X			
E-diary training, dispense digital thermometer and measuring device		X			
Assist the participant with downloading e-diary app, or issue provisioned device, if required		X			
Obtain and record baseline assessment of prespecified systemic events <u>on the day of and prior to vaccination</u> in the e-diary		X			
Administer study intervention		X			
Postvaccination observation (at least 30 minutes) and assessment of immediate events		X			
Collect CD4 count and HIV viral load assessment results at delivery, if not part of standard of care				X	

Visit Description	Screening ^a	Vaccination Visit	1-Month Follow-Up ^b	Delivery ^c	6-Month Postdelivery
Visit Window (Days)		Vaccination Day 1	28 to 42 Days After Vaccination	Delivery	180 to 210 Days After Delivery
Type of Visit	Clinic	Clinic	Clinic, Home, or Telephone	Maternity Unit	Clinic, Home, or Telephone
Delivery blood draw for serologic assessment (~15 mL)				X	
Record pregnancy outcome information				X	
Site review of e-diary data with participant follow-up until ongoing event resolution, if applicable ^f		X-----X		X ^g	
Collect e-diary device/assist participant with deletion of e-diary application from personal device, as appropriate			X	X ^g	
Record AEs, AESIs, and SAEs, as appropriate	X-----X				

- If required prenatal assessments are not routinely performed, prerandomization assessments and test results to confirm maternal participant eligibility for this clinical trial can be obtained and reviewed by the investigator or qualified designee at the screening visit. Syphilis, HBV, and active TB screening and assessment of HIV viral load and CD4 count must be completed within 14 days prior to randomization. If prenatal assessments are routinely performed and syphilis, HBV, and active TB screening results and CD4 count and HIV viral load assessment results have been obtained from a sample collected within 14 days prior to randomization, the screening visit and vaccination visit may take place on the same day, so long as test results are reported prior to study vaccination.
- The 1-month follow-up visit will not be performed if delivery occurs before this visit. Active elicitation and collection of AEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination. Once delivery occurs, the visit windows are calculated based on the delivery date.
- The delivery visit includes the time from when a participant is admitted into labor through discharge following delivery of the participant's infant.
- Where an obstetric ultrasound examination has not been performed at ≥ 18 weeks of pregnancy, perform an ultrasound examination. As part of the obstetric history, details regarding the LMP and EDD are to be recorded.
- Where syphilis, HBV, and active TB screening, and CD4 count and HIV viral load are not routinely monitored as part of standard of care, obtain a sample(s) for local testing. Prerandomization assessments and test results to confirm maternal participant eligibility must be obtained within 14 days prior to randomization.
- Local reactions and systemic events will be captured within the e-diary until the resolution date. After e-diary collection, the site will follow-up with the participant for any ongoing events.
- This assessment is not applicable when the e-diary is collected at the 1-month follow-up visit.

1.3.2. Schedule of Activities for Infant Participants

Visit Description	Birth	1-Month Follow-Up ^a	6-Month Follow-Up ^a
Visit Window (Days)	Birth to 7 Days After Birth	28 to 48 Days After Birth	180 to 210 Days After Birth
Type of Visit	Hospital	Clinic or Home	Clinic, Home, or Telephone
Assign infant participant identifier	X		
Cord blood sample (~10 mL) for serologic assessment ^b	X		
Demography	X		
Collect birth outcome information, including infant's birth data, GA, and Apgar score	X		
Obtain and record infant's length, head circumference, and weight	X	X	X ^c
Physical examination, including vital signs (temperature, heart rate, and respiratory rate), performed within 72 hours after birth	X		
Obtain and record vital signs, including temperature, heart rate, and respiratory rate		X	X ^c
Targeted physical examination (record in the site source document)		X	X ^c
Record immune globulins, monoclonal antibodies (eg, Synagis), or blood products (eg, whole blood, packed cells)	X	X	X
Review eligibility	X		
Record details of ART prescribed for prevention of mother-to-child transmission of HIV	X	X	X
Obtain and record details of childcare/daycare (for infant participants)	X	X	X
Obtain and record details of breastfeeding information (including whether or not the maternal participant is breastfeeding exclusively)	X	X	X
Record results of any standard-of-care HIV testing performed to confirm HIV status	X	X	X
Record AEs, AESIs, NDCMCs, and SAEs, as appropriate	X	X	X

- If medically necessary (eg, during an outbreak, pandemic situation, or natural disaster), study visits that cannot be conducted in the clinic or at home, in accordance with the protocol requirements, may be conducted via telephone.
- Cord blood must be obtained on the day of birth. Cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been clamped and cut. If cord blood is unavailable, a blood sample may be collected from the infant participant preferably within the first 24 hours but up to 7 days after birth. The infant's weight must be used to determine the volume of blood that can be collected.
- Assessments are collected with clinic and home visits, as appropriate, and are not applicable when the visit is conducted via telephone.

2. INTRODUCTION

Prevention of RSV disease in young infants is a significant unmet medical need globally. For infants, RSV is the leading cause of bronchiolitis and viral pneumonia, 2 pathologies that can lead to fatal respiratory distress, especially in infants living with risk factors, including prematurity, underlying cardiopulmonary disease, or ineffective healthcare systems.¹ Maternal HIV infection is a well-established risk factor for RSV disease, as HIV-infected pregnant women experience a higher incidence of RSV infection both during pregnancy and postpartum.² HIV-exposed but uninfected infants appear to be at a higher risk for severe RSV disease, suffering higher rates of hospitalization and death due to LRTI-RSV when compared to HIV-unexposed, uninfected infants.³ Transplacental transfer of anti-RSV antibodies likely contributes to the increased risk of RSV disease in mothers living with HIV and their infants.^{4,5}

Currently, there is neither specific treatment for RSV infection nor a vaccine to protect infants against RSV disease. Currently, for infants with RSV disease, treatment consists primarily of supportive care. Palivizumab, a human monoclonal antibody targeting the RSV F glycoprotein, is available for prevention of severe RSV disease in young infants at increased risk.^{6,7} However, the high cost and monthly injection requirement of palivizumab have limited its use to very premature and at-risk infants in select geographic regions.^{8,9,10,11}

The protective effect of palivizumab, however, offered a proof of concept for a vaccine directed against the RSV F protein. There are 2 antigenic variants of RSV, namely, RSV subgroup A (RSV A) and RSV subgroup B (RSV B).¹² The RSV vaccine being investigated in this study is a bivalent vaccine composed of stable RSV prefusion F antigens representing the 2 subgroups to help ensure the broadest coverage against RSV illness. The pivotal Phase 3 C3671008 study found that, when administered to healthy pregnant participants between 24 and 36 weeks' gestation, RSVpreF was 81.8% and 69.4% effective against severe MA-LRTI in infants through 3 and 6 months of life, respectively.¹³

2.1. Study Rationale

Maternal immunization offers an attractive strategy for infant disease prevention. Phase 1/2 studies in healthy nonpregnant adults, and a pivotal Phase 3 study in pregnant participants, have demonstrated acceptable tolerability and safety of RSVpreF.¹³ In the Phase 1/2 studies, a robust immune response was observed 1 month after vaccination. The combined RSV A and B serum neutralization GMTs have been shown to be 12 to 20 times higher than those with 100 µg/mL of palivizumab, the concentration of the monoclonal antibody that is known to provide near to complete protection of high-risk infants from severe RSV disease.¹⁴ In Pfizer's Phase 3 study in healthy pregnant participants, RSVpreF met prespecified efficacy criteria for the prevention of MA-LRTI in infants.

Globally, nearly 1000 women are newly infected with HIV daily, though the widespread access to ART¹⁵ has reduced vertical HIV transmission. HIV-exposed but uninfected infants suffer greater morbidity and mortality from RSV infection than their HIV-unexposed counterparts.¹⁶ This may be related in part to reduced transplacental transfer of maternal antibodies. This randomized, double-blinded, placebo-controlled study is designed to

evaluate Pfizer's RSVpreF in a cohort of HIV-infected pregnant participants, and assess the vaccine's safety, tolerability, and immunogenicity in the setting of maternal HIV infection. Evaluating RSVpreF in this population is critical given the additive effect of HIV infection to the global burden of infant RSV disease. Transplacental transfer of RSV-neutralizing antibodies was reduced in 2 studies of newborns born to HIV-infected pregnant women.^{4,5} Mitigation of this effect was seen with maternal viral suppression, use of combination ART, and absence of hypergammaglobulinemia, though with limited data.^{4,5} Maternal HIV infection has also been associated with reduced immune responses and disease protection with maternal influenza vaccination.¹⁷ Descriptive immunogenicity will elucidate possible attenuating effects of HIV infection on immune responses to RSVpreF.^{4,5,18,19}

2.2. Background

The vaccine investigated in this study is a bivalent RSV prefusion F subunit vaccine (RSVpreF) developed by Pfizer. The RSV F glycoprotein facilitates fusion of the virion and host cell membrane through a dramatic transition from an unstable but highly immunogenic prefusion conformation to the more stable postfusion state.²⁰ Preclinical studies show that prefusion F elicits much higher neutralizing antibody titers than postfusion F, and that the most potent neutralizing antibodies from postinfection human sera target the prefusion form.²¹ RSVpreF is composed of engineered, stabilized, trimeric, prefusion F glycoproteins matching the 2 subgroups (RSV A and B) to help ensure the broadest coverage against RSV illness.

RSVpreF development started with 2 indications using the same antigens, dose, and formulation:

- **Older Adult:** Prevention of LRTI-RSV in adults 60 years of age and older via active immunization.
- **Maternal:** Prevention of LRTI-RSV and severe LRTI-RSV in infants from birth through 6 months of age via active immunization of pregnant individuals.

Pfizer's Phase 1 and 2 studies demonstrated proof that RSVpreF elicits robust neutralizing antibodies in adults that persisted for at least 12 months after vaccination (Studies C3671001 and C3671002) and that a single 120-µg dose of RSVpreF had 100% observed efficacy against RT-PCR–confirmed symptomatic RSV infection in a human challenge model (Study WI257521). Proof that the vaccine is efficacious in preventing LRTI caused by RSV in older adults ≥60 years of age was demonstrated in a multinational Phase 3 study (Study C3671013).²² Protection against LRTI-RSV defined by 2 or more symptoms demonstrated a 66.7% VE. A VE of 85.7% was observed in participants with the primary endpoint of LRTI-RSV defined by 3 or more RSV-associated symptoms. On 31 May 2023, based on efficacy and safety data from this older adult population study (C3671013), the FDA approved RSVpreF (Abrysvo™) for individuals 60 years of age and older in the US.²³ Additionally, the Phase 3 maternal population study (C3671008) recently demonstrated efficacy in preventing RSV-associated severe LRTI in infants born to mothers who received

RSVpreF. Establishing the safety and efficacy profile of RSVpreF in older adults was foundational for protecting infants via maternal vaccination.

2.2.1. Clinical Overview

Adult Program Studies

The older adult program includes 2 Phase 1/2 studies, 3 Phase 3 studies, and a Phase 2a human challenge study.

- In the completed Phase 1/2 Study C3671001, 1233 healthy adults 18 through 49 and 50 through 85 years of age received the 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg), with or without Al(OH)₃, or placebo, administered with or without concomitant influenza vaccine. The results have shown that the vaccine was well tolerated and immunogenic in both age groups. RSVpreF elicited robust neutralizing responses against RSV A and RSV B 1 month after vaccination for both age groups across all vaccine dose levels and formulations; these responses remained high through the 12 months after vaccination. RSVpreF was safe and well tolerated when administered alone or with SIIV, with no major differences observed across all dose levels and formulations. Most reported local reactions or systemic events were mild or moderate in severity. The proportions of participants reporting AEs were generally similar across RSVpreF groups, and no SAEs were considered related to the investigational vaccine.
- In the completed Phase 1/2 Study C3671002, 250 older adults 65 through 85 years of age received the 3 dose levels of RSVpreF with Al(OH)₃ or CpG/Al(OH)₃ (60 µg, 120 µg, and 240 µg), given as a single dose or on a schedule of 2 doses administered 2 months apart. All RSVpreF doses and formulations elicited high RSV A– and RSV B– neutralizing antibody GMTs 1 month after vaccination (GMFRs ranging from 4.8 to 11.6 and 4.5 to 14.1, respectively). CpG-containing formulations did not further increase neutralizing GMTs compared to RSVpreF with or without Al(OH)₃. GMTs in all groups declined but remained higher than baseline (before vaccination) and placebo (SIIV only) 12 months after vaccination (GMFRs ranging from 2.1 to 3.5 and 2.2 to 4.3, respectively). No increase in GMTs was observed 1 month after Vaccination 2 (GMFR of 0.9). All doses and formulations were safe and well tolerated.
- Study C3671014 is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind, lot-consistency study in a population of up to 1000 healthy adults 18 to ≤49 years of age. The study examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120-µg dose to healthy adults. The primary analyses showed that the ratios of neutralizing GMTs for the 3 manufactured RSVpreF lots 1 month after vaccination were equivalent, and that the 120-µg dose of RSVpreF was well tolerated and had an acceptable safety profile.

- A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, immunogenicity, and efficacy of an RSV vaccine (RSVpreF) in a virus challenge model in healthy adults (NCT04785612) was conducted by hVIVO in 70 healthy participants 18 to 50 years of age. Participants received a single dose of either RSVpreF 120 µg or placebo, and 4 weeks later underwent intranasal challenge with RSV-A Memphis 37b virus. The immunogenicity and efficacy of RSVpreF vaccination on virus replication, clinical symptoms, and incidence of symptomatic RSV infection following the intranasal challenge were evaluated. The primary analysis of the human challenge study showed that a 120-µg dose of RSVpreF was well tolerated and had an acceptable safety profile. The completed study demonstrated 100% efficacy of RSVpreF against RT-PCR–confirmed symptomatic infection.
- Study C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety, immunogenicity, and efficacy of Pfizer's RSVpreF in prevention of RSV-associated LRTI in adults 60 years of age and older. Both healthy adults and adults with stable chronic cardiopulmonary conditions are included. Approximately 10% of participants with stable chronic cardiopulmonary conditions such as COPD, asthma, or CHF have been enrolled. The study enrolled over 37,000 participants, randomized to receive RSVpreF or placebo in a 1:1 ratio. This is an event-driven study with a target of 59 first episodes of evaluable RSV-associated LRTI cases. Interim analysis results in August 2022 showed protection against LRTI-RSV defined by 2 or more symptoms, with VE of 66.7%. VE of 85.7% was observed in participants with a more severe disease primary endpoint of LRTI-RSV defined by analysis of 3 or more RSV-associated symptoms. The vaccine was well tolerated, with no safety concerns. On 31 May 2023, the FDA approved RSVpreF (Abrysvo) for individuals 60 years of age and older in the United States.²³
- Study C3671006 is a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study. 1403 healthy adults ≥65 years of age were randomized in a 1:1 ratio to either a coadministration group or a sequential-administration group. The intention of this study was to demonstrate that the immune responses generated when a 120-µg RSVpreF dose was coadministered with SIIV were noninferior to the immune responses when these products were administered 4 weeks apart. The safety and tolerability of RSVpreF were also examined. Results demonstrated noninferiority of the RSVpreF and SIIV immune responses when RSVpreF was coadministered with SIIV. The results of this completed study support the acceptability of coadministration of RSVpreF and SIIV in an older adult population.
- Study C3671016, an ongoing Phase 1/2/3 study in participants 2 to <18 years of age at high risk of RSV disease that was initiated in June 2023. The study will consist of 2 phases: Phase 1 and Phase 2/3. Phase 1 is an open-label, age-descending, dose-finding study and Phase 2/3 is a placebo-controlled, randomized, double-blinded study to evaluate the safety, tolerability, and immunogenicity of RSVpreF. Both the 120-µg and 60-µg dose will be evaluated. Up to 120 participants are expected to be enrolled in the Phase 1 cohort and up to 1860 participants will be enrolled in the Phase 2/3 cohort.

- Study C3671023 is an ongoing Phase 3 study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults at high risk of severe RSV disease in 2 distinct patient populations. Study C3671023 – Substudy A is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults 18 to <60 years of age considered to be at high risk of RSV disease due to certain chronic medical conditions, and Study C3671023 – Substudy B is a Phase 3, single-arm, open-label, multicenter study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in immunocompromised adults. The 120-μg dose will be evaluated in both substudies.

Maternal Participant Program Studies

RSVpreF is also being studied in the maternal program, which includes Phase 2b studies and a Phase 3 study in nonpregnant and pregnant participants, respectively.¹³

- Study C3671003 is a completed Phase 2b multicenter, randomized, placebo-controlled study in up to 650 healthy pregnant participants 18 through 49 years of age who received RSVpreF at 120 μg and 240 μg, formulated with or without Al(OH)₃, or placebo. The completed final analysis provided evidence of the good tolerability and safety of RSVpreF in maternal vaccine recipients, and the safety of maternal vaccination with RSVpreF for the infant led to a dose selection of 120 μg without Al(OH)₃.
- Study C3671004 is a completed Phase 2b study of 713 healthy nonpregnant participants 18 through 49 years of age. A total of 709 participants received RSVpreF 120 μg or RSVpreF 240 μg with Al(OH)₃, or placebo, administered with or without concomitant Tdap. The study demonstrated a good safety and tolerability profile, high immune responses, and noninferiority of the responses to RSV A, RSV B, tetanus, and diphtheria when coadministered with Tdap, with RSV A and RSV B 50% NT GMRs of 0.97 and 0.96, respectively, at 1 month after vaccination.
- Study C3671008 is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against MA-LRTI in infants. Healthy participants ≤49 years of age who are between 24 and 36 weeks of gestation received either RSVpreF 120 μg or placebo. The study enrolled approximately 7400 pregnant individuals. Primary analysis results in September 2022 demonstrated VE of 81.8% against severe MA-LRTI due to RSV in infants from birth through the first 90 days of life, with high efficacy of 69.4% demonstrated through the first 6 months of life. RSVpreF was well tolerated with no safety concerns for both vaccinated individuals and their newborns.

2.3. Benefit/Risk Assessment

RSV is a common cause of respiratory illness among pregnant women and the most common cause of viral pneumonia and bronchiolitis in infants and young children worldwide.²⁴

RSVpreF is being evaluated in ongoing clinical studies. Pfizer's maternal immunization approach circumvents the risk of vaccine-mediated disease enhancement that was observed in the 1960s following direct immunization of RSV-naïve infants with FI-RSV.²⁵ FI-RSV elicited a predominantly nonneutralizing antibody response and a Th2-biased cell-mediated response, both of which are considered potential contributing factors to disease enhancement.²⁶ During preclinical studies, in a standard cotton rat infectious RSV challenge model, FI-RSV showed pathological signs of causing disease enhancement, and the current Pfizer vaccine candidate, RSVpreF, did not. Most important, RSV vaccine-mediated disease enhancement has not been reported to occur in RSV-experienced individuals after immunization with any RSV vaccine candidate. Because pregnant women are universally RSV-experienced, they are not considered at risk for a disease-enhancing immune response to the vaccine that could exacerbate infection in themselves. Enhanced disease has not been observed in infants born to mothers who received prior investigational RSV vaccines; therefore, enhanced disease in infants is very unlikely.¹³

Vaccination with the RSV prefusion F antigens elicits a higher ratio of neutralizing to nonneutralizing antibodies, more closely matching the profile in naturally exposed individuals.¹⁴ The safety profile of RSVpreF observed to date is similar to that of prior RSV F subunit vaccines tested in RSV-experienced adults.^{13,14,27,28}

There are limited data on the global burden of maternal RSV infection. However, in 1 multisite study, RSV-associated disease in pregnancy was shown to result in prolonged hospitalization and an increased likelihood of preterm birth in women who tested RSV-positive.²⁹ HIV infection exacerbates the impact of RSV infection in pregnant women. A study of pregnant women in Kenya found the incidence of RSV illness to be 4 times higher in pregnant women living with HIV when compared to pregnant women without HIV; all of the study's HIV-positive participants were receiving ART but HIV viral loads were not reported.² Though HIV status had no observed effect on the incidence of LRTI-RSV in the infants from this study, vertical transmission has been demonstrated in animal models of RSV infection.³⁰ It is possible that vaccination may benefit the pregnant women who receive it. The benefit of maternal vaccination is accrued to the infant by means of transplacental antibody transfer.³¹

With the lack of direct antiviral therapies for the treatment of RSV disease, the limitation of monoclonal antibody prophylaxis for high-risk infants, and the absence of a licensed vaccine to prevent RSV disease, there exists an unmet medical need for agents that can protect vulnerable infants from RSV disease, and particularly those whose vulnerability may be exacerbated by in-utero HIV exposure.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of IMP may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in [Section 6.1](#) for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RSVpreF		
Pfizer has identified the most common risks for RSVpreF as local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fatigue, headache, diarrhea, joint pain, nausea, vomiting, muscle pain, and fever. Guillain-Barre syndrome has been identified as a potential risk for RSVpreF. Other events of interest include atrial fibrillation, polyneuropathy preterm birth (delivery at <37 0/7 weeks' gestation), and hypertensive disorders of pregnancy. The identified adverse reactions in local product labels may vary depending on the requirements of the respective regulatory authorities (eg, EU-SmPC and USPI).	These are common adverse reactions seen with other vaccines as well as RSVpreF.³² Data available from completed and ongoing studies showed a low incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, and race/ethnicity. In Study C3671013, conducted in adults 60 years of age and older, there was 1 case of Guillain-Barre syndrome and 1 case of Miller Fisher syndrome with a plausible temporal relationship with vaccination. Both cases had confounding factors or alternative etiology. In Study C3671013, conducted in adults 60 years of age and older, there was a nonsignificant numerical imbalance in the number of cases of atrial fibrillation reported for individuals who received RSVpreF compared to individuals who received placebo. Most of the participants who had atrial fibrillation and received RSVpreF had a preexisting medical history of atrial fibrillation and/or cardiac disease. In Study C3671008, conducted in pregnant individuals, there were no statistically meaningful imbalances between RSVpreF and placebo recipients in the overall rates of preterm birth (5.7% [95% CI: 4.9, 6.5] versus 4.7% [95% CI: 4.1, 5.5], respectively). However, a numerical imbalance was observed in upper-middle-income countries between RSVpreF and placebo recipients. Outcomes in the premature infants were similar between the 2 groups. In Study C3671008, conducted in pregnant individuals, there was a nonsignificant numerical imbalance in hypertensive disorders of pregnancy	- The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. - Collection of AEs and SAEs throughout the study. - DMC throughout the study to review all safety data. - All participants will be observed for at least 30 minutes after vaccination. - Specific reference to risks and events of interest is made within the ICD, with reporting instructions if a case is suspected.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reported for participants who received RSVpreF compared to participants who received placebo. The majority of preterm and hypertensive disorders occurred more than 30 days following vaccination.³³	
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled may be:

- Receipt of an RSV vaccine shown to be efficacious in healthy pregnant participants.
- Contributing to research to help others.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with RSVpreF are justified by the anticipated benefits that may be afforded to participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Maternal Participants

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
• To describe the safety profile of RSVpreF in maternal participants living with HIV.	• Prespecified local reactions (pain at the injection site, redness, and swelling) • Prespecified systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) • AEs • AESIs • SAEs	In maternal participants living with HIV receiving 1 dose of the study intervention, the proportion of the following safety events reported: • 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 • AESIs throughout the study • SAEs throughout the study

Objectives	Endpoints	Estimands
Secondary:	Secondary:	Secondary:
To describe the immune responses elicited by RSVpreF in maternal participants living with HIV.	RSV A and RSV B serum NTs	In maternal participants in compliance with the key protocol criteria (evaluable immunogenicity population): - GMT of NTs for RSV A and RSV B at each blood-sampling visit - GMFR of NTs for RSV A and RSV B from before vaccination to the postvaccination blood-sampling visit
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To descriptively compare the immune responses elicited by RSVpreF between pregnant participants living with HIV from this study and pregnant participants without HIV from Study C3671008.	RSV A and RSV B serum NTs	

3.2. Infant Participants

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
To describe the safety profile of RSVpreF.	- Specific birth outcomes - AEs from birth through 1 month of age - SAEs and NDCMCs from birth through 6 months of age	In infant participants born to maternal participants living with HIV receiving 1 dose of the study intervention, the percentage of participants with each safety endpoint
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To evaluate RSV serum NTs elicited by RSVpreF and transferred transplacentally.	RSV A and RSV B serum NTs measured at birth	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF administered to pregnant participants living with HIV, as well as safety and immunogenicity in their infants.

Study-eligible, pregnant participants living with HIV providing informed consent for themselves and their infants will be referred to as "maternal participants" and will receive a single dose of RSVpreF or placebo (1:1 randomization). Follow-up for maternal participants will continue through pregnancy and until 6 months after delivery. Assessments will include evaluations of safety, tolerability, and immunogenicity of the vaccine in maternal participants.

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

To assess immunogenicity, all maternal participants will have blood drawn at baseline, prior to vaccination, and at delivery. Immune responses elicited by RSVpreF in maternal participants in this study will be analyzed and will also be compared to immune responses elicited by RSVpreF in maternal participants in the C3671008 study, in which RSVpreF efficacy was demonstrated.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period, or longer, for ongoing events after study vaccination (ie, from Day 1, the day of vaccination, until resolution). Reported Grade 3 and potentially Grade 4 reactogenicity events will be assessed by the investigator or a qualified designee to determine unscheduled medical visit requirements.

For all maternal participants, AEs will be collected from informed consent through 1 month following study intervention administration. AESIs and SAEs will be collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected.

Infants born to participants who receive the study intervention will be referred to as "infant participants." Infant participants will be followed until 6 months after birth. AEs will be collected from birth through 1 month following birth, and NDCMCs and SAEs will be collected from birth throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected.

4.1.1. Approximate Duration of Participation for Each Participant

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

All eligible infant participants born to enrolled maternal participants will participate in the study from the time of birth and will be followed for up to 6 months after birth.

4.2. Scientific Rationale for Study Design

See [Section 2.1](#).

4.3. Justification for Dose

The dose and formulation of RSVpreF selected for use in this study are based on the safety and immunogenicity data from 3 Phase 1 and 2 studies (Studies C3671001, C3671003, and C3671004). There were no substantial differences observed between the immunogenicity or reactogenicity of the 120-μg and 240-μg dose levels of the formulation without Al(OH)₃ in infant participants born to vaccinated mothers. The 120-μg dose, without any adjuvants, has been shown to have low reactogenicity and an acceptable safety profile in maternal participants dosed in the C3671008 study, and will be the dose given in this study.

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.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population, including, where permitted under local regulations, age, sex, race, and ethnicity. 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 this study only if all of the following criteria apply:

5.1.1. Inclusion Criteria – Maternal Participants

Refer to the ISF for further eligibility details regarding maternal GA at vaccination.

Where study procedures are used to determine eligibility criteria (eg, ultrasound examination, syphilis testing, HBV testing, screening for active TB as per local guidelines, HIV viral load and CD4 count), and are not performed as part of routine prenatal care, they must be performed as part of this clinical trial and reviewed by the investigator or a qualified designee prior to randomization.

HIV viral load and CD4 count must be assessed from samples obtained within **14 days** prior to randomization.

Screening and testing for **syphilis, active TB, and HBV** must be assessed during this pregnancy and prior to randomization.

Each maternal participant must provide informed consent for herself and the unborn infant prior to performing any procedures, including those that are being done exclusively to meet study eligibility criteria, per all applicable requirements.

Age and Sex:

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

Note: The GA must be based upon 1 of the following composite criteria based on the timing and availability of data on the LMP and an ultrasound examination performed in the first or second trimester.³⁴ The earliest ultrasound data available during the current pregnancy should be used. Where the routine practice is for the GA determination to be based upon the first-trimester ultrasound examination alone, without the LMP, this routine practice will be accepted.

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

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

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

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

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

Disease Characteristics:

2. Confirmed stable HIV disease, defined as a documented HIV viral load <1000 copies/mL and CD4 count >200 cells/mm³, within 14 days prior to randomization.
3. Current and stable use of ART for at least 90 days prior to randomization.
4. Receiving prenatal standard of care based on country requirements.
5. Had a fetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed.
6. Determined by medical history, physical examination, and clinical judgment to be appropriate for inclusion in the study.
7. Within 14 days prior to randomization documented:
 - negative syphilis test, and
 - negative HBV surface antigen test, and
 - absence of active TB infection demonstrated by a negative active TB screening performed per local guideline and no current or previous use of anti-TB treatments during this pregnancy.

Other Inclusion Criteria:

8. Capable of giving signed informed consent as described in [Section 10.1.3](#), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Note: If the maternal participant is a minor, the maternal participant's parent(s)/legal guardian must give informed consent in line with all applicable requirements.

9. Participant is willing to give informed consent for the participant's infant to participate in the study.
10. Intention to deliver at a hospital or birthing facility where study procedures can be obtained.
11. Expected to be available for the duration of the study and can be contacted by telephone during study participation.
12. Willing and able to comply with scheduled visits, investigational plan, laboratory tests, and other study procedures.

5.1.2. Inclusion Criteria – Infant Participants

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

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

2. Parent(s)/legal guardian(s) willing and able to comply with scheduled visits, investigational 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 Participant

Medical Conditions:

1. Any medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. Prepregnancy BMI of $>40 \text{ kg/m}^2$. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used.
3. Participant with opportunistic infections or malignancy.
4. History of active chronic viral hepatitis with biochemical evidence of AST or ALT values >5 times the ULN within 6 months before enrollment.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

6. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention or any related vaccine.
7. Current pregnancy resulting from in vitro fertilization.

Note: Participants known to have used clomiphene citrate and/or letrozole with or without IUI are permitted.

8. Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:
 - Preeclampsia, eclampsia, or uncontrolled gestational hypertension.
 - Placental abnormality.
 - Polyhydramnios or oligohydramnios.
 - Significant bleeding or blood clotting disorder.
 - Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism. This also includes disorders of glucose intolerance (eg, diabetes mellitus type 1 or 2) antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent.
 - Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth.
9. Prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following:
 - Prior preterm delivery at ≤ 34 weeks' gestation
 - Prior stillbirth or neonatal death
 - Previous infant with a known genetic disorder or significant congenital anomaly
10. Major illness of the maternal participant or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the maternal or infant participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response (includes positive serologic testing for regional endemic conditions assessed during routine maternal care, as per local standards of care and obstetric recommendations).

11. Non-HIV-associated congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications.

Prior/Concomitant Therapy:

12. Participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation.
13. Participation in any study involving maternal vaccination with an RSV vaccine or RSV monoclonal antibody.

Note: Criterion applies to participants known to have been in receipt of the active vaccine arm.

14. Receipt of monoclonal antibodies within the year prior to enrollment or the use of systemic corticosteroids for >14 days within 28 days prior to study enrollment.

Note: Permitted treatments include the receipt of SARS-CoV-2 monoclonal antibodies, prednisone doses of <20 mg/day for ≤14 days, and inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids.

15. Anti-TB treatment use currently or at any time during this current pregnancy.
16. Current alcohol abuse or illicit drug use.

Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales.

17. Receipt of blood or plasma products or Ig from 60 days before study intervention 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:

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

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

19. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor-delegate employees directly involved in the conduct of the study and their family members.
20. Children or grandchildren who are direct descendants of investigator site staff or sponsor and sponsor-delegate employees directly involved in the conduct of the study.
21. Participants who are breastfeeding at the time of enrollment.

5.2.2. Exclusion Criteria – Infant Participants

1. Infant who is a direct descendant (eg, child or grandchild) of the investigator site staff or sponsor and sponsor delegate employees directly involved in the conduct of the study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

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

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention – Maternal Participants

The following conditions are temporary or self-limiting; a maternal participant may be vaccinated once the condition(s) has/have resolved and if no other exclusion criteria are met.

The prevaccination blood draw and vaccination should take place on the same day. In the event that this is not possible, the prevaccination blood draw is also permissible within 7 days before the vaccination visit.

- Current febrile illness (body temperature $\geq 38^{\circ}\text{C}$ [$\geq 100.4^{\circ}\text{F}$]) or other acute illness within 48 hours before study intervention administration.
- Diagnosed malaria within the last 7 days prior to study intervention administration.

- Receipt of any inactivated vaccine (including licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary or emergency use) within 14 days or any live vaccine within 28 days before study intervention administration.
- If systemic corticosteroids (equivalent of ≥ 20 mg/day of prednisone) have been administered short term (≤ 14 days) for treatment of an acute illness, study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

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

Study Intervention(s)		
Intervention name	RSVpreF	Placebo
Type	Vaccine	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose formulation	The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The RSV drug product will be 120 μg of the RSV prefusion F antigen (60 μg A and 60 μg B). The drug product is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The drug product will be reconstituted by a diluent consisting of sterile water in a PFS. The lyophilized drug product contains excipients that, after reconstitution, will yield a solution as detailed in the IB. The fill volume of the drug product vial and diluent PFS are designed such that the 120-μg vaccine dose is delivered by injecting the entire contents of the syringe.	Placebo will be a lyophile match to the vaccine, which will consist of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients. The placebo is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The lyophilized white cake will be reconstituted by a diluent consisting of sterile water in a PFS. The physical appearance of the reconstituted RSVpreF and placebo will be matched, and the study will be conducted in a double-blinded manner. The fill volume of the placebo vial and diluent PFS is designed such that the intended placebo dose is delivered by injecting the entire contents of the syringe to match the 120-μg vaccine dose.
Unit dose strength(s)	120 μ g	N/A

Study Intervention(s)		
Dosage level(s)	120 µg	N/A
Route of administration	Intramuscular injection	Intramuscular injection
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Study intervention will be provided in a glass vial. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Each vial and PFS will be labeled per country requirement.	
SRSD	IB	IB

Study Arm(s)		
Arm Title	RSVpreF	Placebo
Arm Description	Participants will receive a single dose of RSVpreF (120 µg) in accordance with the IPM.	Participants will receive 1 dose of study intervention in accordance with the IPM.

6.1.1. Administration

Maternal participants will receive 1 dose of the study intervention at the vaccination visit (Day 1) in accordance with the study's SoA. The study intervention will be administered intramuscularly by injecting the entire contents of the syringe into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

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 must be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions will be performed by an appropriately qualified, 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.

Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

In this study, medical devices being deployed are for the reconstitution diluent for the study intervention (RSV vaccine). The study intervention supplies are provided in a kit that contains the study intervention (RSVpreF or placebo lyophilized powder in a vial), a PFS containing sterile water, and a vial adapter.

Instructions for medical device use are provided in the IPM.

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

Please refer to [Section 8.4.9](#) for details.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only maternal participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.
3. 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 temperatures since previously documented upon return to business.
4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery, along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions 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. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM for storage conditions of the study intervention once reconstituted.
6. Study interventions should be stored in their original containers.
7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention 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. A second staff member will verify the dispensing.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information, including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned vaccine group, and DU or container number(s) when the study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study intervention will be dispensed at the study visits summarized in the SoA.

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

6.4. Blinding

This study is a double-blinded study. The physical appearance of RSVpreF and placebo will be matched.

6.4.1. Blinding of Maternal Participants

The maternal participant, and the participant's parent(s)/legal guardian (if a minor), will be blinded.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention as the physical appearance of RSVpreF and placebo will be matched. Please refer to the IPM for further details.

Participants will be assigned to receive the study intervention according to the assigned vaccine group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

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

6.4.3. Blinding of the Sponsor

The majority of sponsor staff will be blinded to study intervention allocation. All laboratory testing personnel performing serological assays will remain blinded to study interventions assigned/received throughout the study.

The following sponsor staff will be unblinded (further details will be provided in the DMC charter and other study documents):

- An unblinded vendor supporting interactions with the DMC. This will comprise a statistician and a programmer(s).

The unblinded safety analysis for the DMC will be performed by Pfizer/vendor programmers who are separate from the study.

6.4.4. Breaking the Blind

The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's vaccine assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

6.5. Study Intervention Compliance

All doses of the study intervention will be administered by the appropriately designated study staff at the investigator site. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in [Section 7.3](#).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety only when associated with an SAE.

6.9. Prior and Concomitant Therapy

6.9.1. Prohibited Concomitant Vaccinations and Treatments – Maternal Participants

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

Note: Licensed vaccines containing **pertussis** (including Tdap) **may not** be coadministered with the study intervention or given within **14 days** after study intervention administration (Day 1 through Day 14), except if medically necessary (eg, during an outbreak- or pandemic-related situation).

Note: Licensed vaccines containing only tetanus toxoid or tetanus diphtheria **may** be coadministered with the study intervention.

- Current or previous use of anti-TB treatments during this pregnancy.

6.9.2. Permitted Concomitant Vaccinations and Treatments – Maternal Participants

- Licensed vaccines (including COVID-19 vaccines authorized for temporary or emergency use) may be given during the study starting 7 days after study intervention administration (Day 8).
- Licensed vaccines containing only tetanus toxoid or tetanus and diphtheria may be coadministered with the study intervention.
- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. Short-term systemic corticosteroid (equivalent of <20 mg/day of prednisone) use for ≤14 days prior to the administration of the study intervention is permitted.
- The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration is permitted during participant participation in the study.

6.9.2.1. Recording Nonstudy Vaccinations and Concomitant Medications – Maternal Participants

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

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

Concomitant medications not meeting the criteria above will be documented in the source notes but not documented on the CRF (eg, supplements, vitamins).

6.9.3. Prohibited Concomitant Vaccinations and Treatments – Infant Participants

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

6.9.4. Permitted Concomitant Vaccinations and Treatments – Infant Participants

- Routine treatments, routine vaccinations, and routine procedures (eg, circumcision) are permitted at any time during the study, in accordance with national recommendations, medical standard of care, or accepted practice.
- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during infant participant participation in the study.
- Local anesthetic may be applied to the site of the blood draw, as appropriate.

6.9.4.1. Recording Nonstudy Vaccinations and Concomitant Medications – Infant Participants

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

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

Concomitant medications not meeting the criteria above will be documented in the source notes but not documented on the CRF (eg, vaccines, supplements, vitamins).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A maternal participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Withdrawal due to reactogenicity;

- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

An infant participant may withdraw from the study at any time at the request of the participant's parent(s) and/or legal guardian(s) or may be withdrawn at any time at the discretion of the investigator.

If a maternal participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such request in the site study records and notify the sponsor accordingly.

If an infant participant is withdrawn from the study, the participant's 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 request in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will 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 PSSA.

Maternal participants who withdraw after randomization will not be replaced.

7.2.1. Withdrawal of Consent

Maternal participants and parent(s)/legal guardian(s) of infant participants born to maternal participants who request to discontinue active study participation (eg, biological sample collection or surveillance for disease endpoints) will remain in the study and must continue to be followed for protocol-specified safety follow-up procedures.

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

information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant 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/attend a required study visit:

- The site must attempt to contact the participant or parent(s) and/or legal guardian(s) and reschedule the missed visit as soon as possible and counsel the participant or parent(s) and/or legal guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant or parent(s) and/or legal guardian(s) wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant or parent(s) and/or legal guardian(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant or parent(s) and/or legal guardian(s) continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

The year of birth for maternal participants, and the date of birth for infant participants, will be collected to critically evaluate the immune response and safety profile by age.

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

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that 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 they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

8.1.1. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described in the SoA.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.1.2. Home Health Visits

A home health visit may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. Assessments that may be performed during a home health visit are described in the SoA.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

8.2. Immunogenicity Assessments

8.2.1. Total Volume of Blood Collected – Maternal Participants

The total volume of blood collected for antibody assessment over the course of the study will be approximately 30 mL (~15 mL/visit). Additional blood sample(s) may be required to perform syphilis, HBV, and active TB screening, and CD4 count and HIV viral load assessment.

For all maternal participants, other additional blood samples may be taken for safety assessments, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.2.2. Total Volume of Blood Collected – Infant Participants

Blood samples will be collected according to the directive 2001/20/EC: Ethical Consideration for Clinical Trials on Medicinal Product Conducted With Minors.³⁵

All infants will have a cord blood sample collected at birth. The cord blood is collected from the umbilical cord vein attached to the placenta after the umbilical cord has been clamped and cut. Blood should be collected as soon as feasible after birth to minimize coagulation and maximize volume. **The total volume of cord blood to be collected for antibody assessment in this study will be 10 mL.**

If a cord blood sample is unavailable, a blood sample may be collected from the infant participant up to 7 days after birth but **preferably within 24 hours after birth**. The infant's weight must be used to determine the volume of blood that can be collected, with the maximum volume of blood collected from the infant to be no more than 5 mL (see Table 1).

Table 1. Guideline for Infant Blood Draw if Cord Blood Sample Was Not Obtained

Body Weight (in kg)	Approximate Volume of Blood (in mL)
<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

8.2.3. RSV Vaccine Antibody Testing – Maternal and Infant Participants

Maternal serum samples (prevaccination/time of delivery) and infant cord blood samples collected will be assayed for RSV A and RSV B serum NTs. Maternal serum samples collected may be tested for Ig levels against nonvaccine RSV antigens to assess natural RSV exposure.

RSV A and RSV B serum NTs will be determined and reported as the NT.

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

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

Samples remaining after completion of the planned assays from blood draws taken throughout the study may be used for additional vaccine and infectious disease-related research. Samples may also be used for assay development, standardization, qualification, and validation. This work is critical in the development, qualification, and validation of serological assays and is required by regulatory authorities for their use in the licensure of a vaccine.

8.2.5. Biological Samples – Maternal and Infant Participants

Samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. 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 vaccines or vaccine-related 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 their samples, or the infant participant's parent(s) and/or legal guardian(s) may request that their 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 participant's DNA is performed.

8.3. Safety Assessments

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

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

8.3.1. Physical Examinations

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE ([Section 10.2](#)) must be reported according to the processes in [Section 8.4.1](#) through [8.4.3](#).

8.3.2. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE ([Section 10.2](#)) must be reported according to the processes in [Section 8.4.1](#) through [8.4.3](#).

8.3.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.3.4. Participant Electronic Diary – Maternal Participants

For all maternal participants, prespecified local reactions and systemic events will be collected for 7 days or longer for ongoing events after study vaccination, where Day 1 is the day of vaccination.

Maternal participants will be required to use an e-diary, installed on a provisioned device or as an application on a personal device, and will be asked to monitor and record local reactions, systemic events, and temperature daily for 7 days or longer following vaccination (Day 1 is the day of vaccination).

On the day of vaccination and prior to vaccination, a baseline assessment of prespecified systemic events will be recorded in the e-diary.

The e-diary allows recording of assessments each day, thus providing the accurate representation of the maternal participant's experience.

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

- If a maternal participant withdraws because of prespecified event(s) recorded in the e-diary, the event(s) should be recorded on the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.
- The investigator or designee must obtain stop dates for any local reactions or systemic events ongoing at Day 7 through resolution. The stop dates should be documented in the source documents and the information entered in the CRF.

Investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate maternal participant compliance and as part of the ongoing safety review. These prospectively collected occurrences of local reactions and systemic events are graded as described in [Section 8.3.4.1](#) and [Section 8.3.4.2](#).

8.3.4.1. Local Reactions – Maternal Participants

Following vaccination (Day 1 is the day of vaccination), the maternal participant or the participant's parent(s)/legal guardian (if a minor) will be asked to assess redness, swelling, and pain at the injection site, and to record the events in the e-diary or appropriate device daily, based on local practice.

Redness and swelling will be measured by the maternal participant and recorded in measuring device units in the e-diary (range: 1 to 21). **Note:** an entry in the e-diary of 21 will be used to denote measurements ≥ 21 . Measurements will be 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 will be prompted to contact the investigator to perform an unscheduled visit to assess the reaction or may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant or the participant's parent(s)/legal guardian (if a minor).

Only an investigator or a qualified designee is able to classify a maternal participant's local reaction as Grade 4, after clinical evaluation of the maternal participant, 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 local reaction, the investigator must immediately notify the sponsor. A Grade 4 reaction will be collected on the CRF.

The site staff will educate the maternal participant and the participant's parent(s)/legal guardian (if a minor) regarding signs and symptoms that would prompt site contact.

If a local reaction persists beyond the end of the 7-day e-diary follow-up period, the maternal participant or the participant's parent(s)/legal guardian (if a minor) will be requested to report that information and/or any new events that develop to the investigator, or the study staff. The investigational site staff will continue to contact the maternal participant to assess and record the information until resolution. 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 or qualified designee is able to classify a maternal participant's local reaction as Grade 4, after clinical evaluation of the maternal participant, documentation from another medically qualified source (eg, emergency room or hospital record), or contact with the maternal participant or the participant's parent(s)/legal guardian (if a minor). Grade 4 local reactions will be collected on the CRF and assessed by the investigator or qualified designee.

8.3.4.2. Systemic Events – Maternal Participants

Prior to vaccination on Day 1, a baseline assessment of fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain will be recorded in the e-diary.

Following vaccination (Day 1 is the day of vaccination), maternal participants or their parent(s)/legal guardian (if a minor) will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain, and to record the events in the e-diary daily, based on local practice.

The events will be assessed by the maternal participant according to the grading scale in [Table 3](#). A maternal participant with severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain will be prompted to contact the investigator to perform an unscheduled visit to assess the systemic event or may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant or the participant's parent(s)/legal guardian (if a minor).

Maternal participants and their parents/legal guardians (if a minor) will also be instructed to contact site staff if they visit the emergency room or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain within 7 days after vaccination.

Based on local practice in certain countries/locales, maternal participants may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as appropriate. In the event that the maternal participant does not call, the investigator or qualified designee will contact the maternal participant or the participant's parent(s)/legal guardian (if a minor). The study staff may also contact the maternal participant or the participant's parent(s)/legal guardian (if a minor) to obtain additional information on events entered into the e-diary.

Only an investigator or qualified designee is able to classify a maternal participant's systemic event as Grade 4, after clinical evaluation of the maternal participant, documentation from another medically qualified source (eg, emergency room or hospital record), or contact with the maternal participant. If a maternal participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected on the CRF.

Further, if a systemic event persists beyond the end of the 7-day e-diary follow-up period, the maternal participant or the participant's parent(s)/legal guardian (if a minor) will be requested to report that information and/or any new events that develop to the investigator, or the study staff. The investigational site staff will continue to call or visit the maternal participant to assess and record the information until resolution, as per local practice. The investigator will enter this additional information in the maternal participant's source notes and CRF.

Table 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 IV 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

Table 3. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4^a
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

- a. Only an investigator or qualified designee is able to classify a maternal participant's systemic event as Grade 4, after clinical evaluation of the maternal participant, documentation from another medically qualified source (eg, emergency room or hospital record), or contact with the maternal participant or the participant's parent(s)/legal guardian (if a minor). Grade 4 systemic events will be collected on the CRF and assessed by the investigator or qualified designee.

8.3.4.3. Temperature – Maternal Participants

A digital thermometer will be given to the maternal participant with instructions on how to measure oral temperature at home, in degrees Celsius. Temperature will be collected for 7 days or longer for ongoing events following vaccination (Day 1 is the day of vaccination).

Fever is defined as an oral temperature of $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$). The highest temperature for each day will be recorded in the e-diary, where possible.

In the event of a fever on the last day the diary was completed, temperature will be measured daily until fever has resolved (1 day of temperature $< 38.0^{\circ}\text{C}$ [$< 100.4^{\circ}\text{F}$]) in order to collect a stop date in the CRF.

A maternal participant with a fever $> 38.9^{\circ}\text{C}$ ($> 102.0^{\circ}\text{F}$) will be prompted to contact the investigator. Based on local practice in certain countries/locales, maternal participants may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as applicable. In the event that the maternal participant does not call, the investigator or a qualified designee will contact the maternal participant or the participant's parent(s)/legal guardian (if a minor). The investigator or qualified designee will assess the fever and perform an unscheduled visit as appropriate.

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

Temperature will be measured and recorded to 1 decimal place and then categorized during analysis as mild, moderate, or severe, based on the intensity grading scale provided in Table 4.

Table 4. Ranges for Fever

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

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

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in [Section 10.2](#).

The definitions of device-related safety events (ADEs and SADEs) can be found in [Section 10.4](#). Device deficiencies are covered in [Section 8.4.9](#).

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other HCPs (clinical signs, test results, etc).

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue from the study intervention (see [Section 7.1](#)).

During the active collection period as described in [Section 8.4.1](#), each maternal participant or the participant's parent(s)/legal guardian (if a minor) and parent/legal guardian/legally authorized representative of an infant participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

Maternal Participants

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each maternal participant, including the participant’s fetus, begins from the time the maternal participant, or the participant’s parent(s)/legal guardian (if a minor), provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving the study intervention, through and including a minimum of 28 calendar days after the last administration of the study intervention.

In this study, the investigator and site staff will ensure the active elicitation and collection of safety events as detailed below:

- The active collection period for nonserious AEs begins once informed consent has been provided and continues through a minimum of 28 calendar days after vaccination.
- The active collection period for AESIs and SAEs begins once informed consent has been provided until the maternal participant completes the study.
- AEs occurring up to 48 hours after blood draws that are related to study procedures must be reported in the CRF.

Infant Participants

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

- The active collection period for nonserious AEs begins at birth and continues through and including a minimum of 28 calendar days after birth.
- The active collection period for AESIs, NDCMCs, and SAEs begins at birth and continues through the last study visit.
- AEs occurring up to 48 hours after blood draws that are related to study procedures must be reported in the CRF.

For Both Maternal and Infant Participants

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

If the maternal participant or the participant's parent(s)/legal guardian (if a minor), or the parent(s)/legal guardian(s) of infant participants born to maternal participants, withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues from the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the PSSA.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer via the PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in [Section 8.4.1](#) are reported to Pfizer Safety via the PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Section 10.2](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in [Section 8.4.1](#), will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the maternal participant or the participant's parent(s)/legal guardian (if a minor) or the parent(s)/legal guardian(s) of infant participants born to maternal participants.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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 [Section 10.2](#).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the maternal participant or the participant's parent(s)/legal guardian (if a minor) or the parent(s)/legal guardian(s) of infant participants born to maternal participants is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in [Section 10.2](#).

8.4.4. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include HCPs, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A participant in this study that becomes pregnant during the period from delivery to the end of their last study visit.
- A female **nonparticipant** is found to be pregnant while being exposed or having been exposed to study intervention **because of environmental exposure**. Below are examples of environmental EDP:
- A female family member or HCP, or other female, reports that she is pregnant after having been exposed to the study intervention by, eg, ingestion, inhalation, or skin contact.
- A male who has been exposed to the study intervention by, eg, ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred.

The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in the setting of environmental exposure, the investigator must report the information to Pfizer Safety via the PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the ISF.
- If a subsequent pregnancy occurs to a maternal participant during the study period, the investigator must report the information to Pfizer Safety via the PSSA. However, the information is not recorded on a CRF unless an abnormal pregnancy outcome occurs (see details below). A copy of the complete report is maintained in the ISF.

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 report.

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).

Abnormal pregnancy outcomes are considered SAEs. 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 follows:

- Spontaneous abortion, including miscarriage and missed abortion, should be reported as an SAE;
- 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 study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

Note: Subsequent maternal exposures with impacted infant will be reported to the sponsor.

8.4.5.2. Exposure During Breastfeeding

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

Scenarios of EDB for infants not delivered during the study must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, via the PSSA. This includes breast milk donation to an infant other than the participant in this study.

Environmental EDB occurs when a female nonparticipant is found to be breastfeeding while being exposed or having been exposed to the study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or HCP who reports that she is breastfeeding after having been exposed to the study intervention by, eg, ingestion, inhalation, or skin contact.

The investigator must report the EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported via the PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the ISF.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness via the PSSA, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the ISF.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs for infant participants:³⁶

- Preterm birth (born at <37 0/7 weeks' gestation)
- Birth weight 1001 to 2500 g
- Developmental delay*

The following AESIs are to be reported as SAEs:

- Extremely preterm birth (born at <28 0/7 weeks' gestation)
- Extremely low birth weight (≤ 1000 g)

Events identified as both an AESI and an NDCMC should be reported as an AESI in the CRF.

*Developmental delay is to be assessed by clinical expertise using local guidelines for standard of care.

AESIs for maternal participants:

- Preterm delivery (delivery at <37 0/7 weeks' gestation)
- Diagnosis of Guillain-Barre syndrome
- Diagnosis of acute polyneuropathy without an underlying etiology
- Hypertensive disorders of pregnancy
- Atrial fibrillation

Details of the AESIs for both infant and maternal participants listed above are further defined in the ISF.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in [Section 8.4.1](#) through [8.4.4](#). An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported via the PSSA. The active collection period for AESIs is from the signing of the ICD until the end of the study for maternal participants, and from birth until the end of the study for infant participants.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in [Section 6.1.2](#). In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in [Section 10.4](#).

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in [Section 8.4.1](#) through [8.4.4](#) and [Section 10.2](#) of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

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

Refer to [Section 10.4.4](#) for instructions for documenting and reporting medical device deficiencies.

8.4.9.2. Regulatory Reporting Requirements for Device Deficiencies

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

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

Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

8.4.10. Vaccination Errors

Vaccination errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Vaccination errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the AE Page of the CRF	Reported on the PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Vaccination errors include:

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such vaccination errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a vaccination dosing error, the sponsor should be notified within 24 hours. Vaccination errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE**.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in [Section 8.2](#).

8.9. Health Economics

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

8.10. Procedures – Maternal Participants

8.10.1. Maternal Participant: Screening Visit (Clinic)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or their parent(s)/legal guardian (if a minor). Each signature on the ICD must be personally dated by the signatory.

A copy of the signed and dated ICD must be given to the maternal participant and the participant's parent(s)/legal guardian (if a minor). **The source data must reflect that the informed consent was obtained before participation in the study.**

If the maternal participant is found ineligible for the study based on a full assessment of the inclusion and exclusion criteria, the investigator may advise the participant and the participant's parent(s)/legal guardian (if a minor), either by telephone or face to face, that the participant will be excluded from further participation in the study.

All eligible maternal participants will proceed to complete the screening and vaccination visit.

Standard-of-care procedures performed **prior to informed consent** can be considered for use in the study, provided they follow guidance around the timing of procedures stipulated in the protocol.

Note: Screening visit and vaccination visit may take place on the same day when all prenatal assessments required to confirm maternal participant eligibility have been performed and reviewed for eligibility within the required study visit window(s).

Note: In countries/locales where procedures to confirm maternal participant eligibility for this clinical trial are not routinely performed, the procedures must be obtained and reviewed by the investigator or qualified designee prior to vaccination. Syphilis, HBV, and active TB screening per local guidelines, HIV viral load and CD4 count assessment must be completed from samples collected within 14 days prior to randomization.

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

The following procedures will be performed:

- Obtain written informed consent, and assent if appropriate, from the maternal participant or the participant's parent(s)/legal guardian (if a minor), before performing any study-specific procedures.
- Assign a single participant identifier using the IRT system.
- Obtain and record the maternal participant demography (including year of birth, sex, race, racial designation, and ethnicity). The year of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record current/former alcohol, tobacco, marijuana, or any illicit drug usage.
- Obtain and record any medical, surgical, and obstetric history of clinical significance, including history from prior and current pregnancy(ies).
- Record the LMP and EDD.
- Record the prepregnancy BMI in the source documentation. If the prepregnancy BMI is not available, record the BMI at the time of the first obstetric visit during the current pregnancy.
- Perform obstetric examination, including but not limited to fetal heart tones and fetal movement.
- Where an obstetric ultrasound examination is not performed at ≥ 18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination.

Note: Physical or obstetric examinations performed as standard of care may be admissible if performed **within 7 days** prior to the vaccination visit. Significant medical and surgical history and abnormal observations from the physical examination will be documented and recorded in the CRF.

- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given at any time during the current pregnancy.
- Obtain details of any nonstudy vaccinations given at any time during the current pregnancy.
- If available, record standard-of-care syphilis and HBV test results obtained from sample(s) taken within 14 days prior to randomization.
- If available, record standard-of-care details of TB infection status from sample(s) taken within 14 days prior to randomization.
- If available, record standard-of-care CD4 count and HIV viral load assessment results. Results must be obtained from sample(s) taken within 14 days prior to randomization.

Note: If CD4 count and HIV viral load assessment, and syphilis, HBV and/or active TB screening are not performed as standard of care, assessments should be performed as part of the study, locally, and vaccination of maternal participants should be deferred until the results are available. Results **must be obtained from sample(s) taken within 14 days prior to randomization.**

- Record details of antiretroviral treatment regimen given at any time during the current pregnancy.
- Remind maternal participants or their parent(s)/legal guardian (if a minor) to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in [Section 8.4](#) and [Section 10.2](#).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Maternal participants or their parent(s)/legal guardian (if a minor) will be instructed to contact the site to report any significant illness (new or worsening), medically attended visit, or any hospitalization that occurs during the study period as detailed in [Section 10.2.3](#).
- Request the maternal participant or the participant's parent(s)/legal guardian (if a minor) to contact the site when the participant goes into labor/is admitted to the maternal unit (The study staff may contact the maternal participant prior to the next study visit to remind the participant, if applicable).

8.10.2. Maternal Participant: Vaccination Visit (Clinic; Day 1 – Visit 1)

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

- Obtain and record CD4 count and HIV viral load assessment results, and syphilis, HBV, and/or active TB screening results. **Prevaccination results must be obtained from sample(s) taken within 14 days prior to randomization.**
- Measure and record vital signs, including body temperature, seated blood pressure, and heart rate.
- Perform a targeted physical examination evaluating/noting any clinically significant abnormalities within the following body systems:
 - **Mandatory:** general appearance; heart; lungs; abdomen
 - **Discretionary:** skin; head, eyes, ears, nose, and throat; musculoskeletal; extremities; neurological; lymph nodes

Note: Significant medical and abnormal observations from the physical examination will be documented and recorded in the CRF.

- Perform an obstetric examination, including but not limited to fetal heart tones and fetal movement.
- Where an obstetric ultrasound examination is not performed at ≥ 18 weeks of pregnancy as part of prenatal standard of care, perform an ultrasound examination.

Note: Physical or obstetric examinations performed as standard of care may be admissible if performed **within 7 days** prior to the vaccination visit, with the exception of fetal heart tones, which **MUST** be performed on the day of vaccination (prior to vaccination).

- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given at any time during the current pregnancy.
- Record details of any nonstudy vaccinations given since the last visit.
- Record antiretroviral treatment since the last visit.
- **Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.**

- Ensure that the maternal participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Assist the participant in downloading the study application onto the participant's own device or issue a provisioned device, if required, and provide instructions on its completion (as applicable).

Note: E-diary completion instructions may be provided to the maternal participant's parent(s)/legal guardian (if a minor).

- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures and provide instructions on their use to the maternal participant or the participant's parent(s)/legal guardian (if a minor).
- **On the day of vaccination, prior to vaccination,** the maternal participant is to complete the baseline e-diary assessment, including systemic event measurements.
- Prior to vaccination, collect a blood sample of approximately 15 mL for serologic assessments (prevaccination blood collection should take place on the same day or within 7 days before the vaccination visit).
- Obtain the maternal participant's randomization number and study intervention kit number using the IRT system. Refer to the IRT manual for further instructions on this process.
- Qualified site staff member(s) will administer a single-vial dose of the study intervention into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IPM for further instruction on this procedure.
- Site staff must observe the maternal participant for any acute reactions for at least 30 minutes after study intervention administration.
- Record any acute reactions in the maternal participant's source documents, on the CRF, and on the PSSA as applicable.
- Ask the maternal participant to complete the e-diary from Day 1 through Day 7, or longer, until any events that are ongoing are resolved, with Day 1 being the day of vaccination.
- Ask the maternal participant or the participant's parent(s)/legal guardian (if a minor) to contact the site staff or investigator immediately if she experiences any of the following from Day 1 through Day 7 after vaccination to determine if an unscheduled reactogenicity visit is required as detailed in [Section 8.10.6](#). The maternal participant may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns as detailed in [Section 8.10.6](#).

- Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$)
- Redness or swelling at the injection site measuring >20 measuring device units (greater than 10 cm)
- Severe pain at the injection site
- Any severe systemic event
- Remind maternal participants or the participant's parent(s)/legal guardian (if a minor) that the study staff may contact them to obtain additional information on events entered into the e-diary until they resolve.
- Remind maternal participants or their parent(s)/legal guardian (if a minor) to inform the study staff of any AEs and SAEs that occur for the duration of the trial as described in [Section 8.4](#) and [Section 10.2](#).
- Remind the maternal participant or the participant's parent(s)/legal guardian (if a minor) to bring the completed e-diary to the next visit (if applicable).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs, and the dispenser/administrator completes the study intervention accountability records.
- The investigator or an appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.
- Maternal participants or their parent(s)/legal guardian (if a minor) will be instructed to contact the site to report any significant illness (new or worsening), medically attended visit, or any hospitalization that occurs during the study period as detailed in [Section 10.2.3](#).
- Request the maternal participant or the participant's parent(s)/legal guardian (if a minor) to contact the site if she goes into labor/is admitted to the maternal unit (the study staff may contact the maternal participant prior to the next study visit to remind her, if applicable).

8.10.3. Maternal Participant: 1-Month Follow-Up Visit (Clinic, Home, or Telephone; 28 to 42 Days After Vaccination)

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

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in [Section 7.2](#).

- Obtain details of any antenatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [Rho(D) immune globulin, eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given since the last visit.
- Review the participant's e-diary data and record assessment in the CRF. Assess compliance and collect stop dates for any local reaction or systemic event ongoing since the 7-day follow-up period after vaccination. Document in the CRF.
 - For any ongoing local reactions or systemic events, the site will follow up until resolution and document and record stop dates in the CRF.
- Collect the sponsor-provisioned e-diary/assist the participant with removing the e-diary study application from personal device.
 - Ensure that all data have been transferred before deactivating the e-diary or deleting the application.
- Remind maternal participants or the participant's parent(s)/legal guardian (if a minor) that the study staff may contact them to obtain additional information on events entered into the e-diary until they resolve.
- If available, record standard-of-care CD4 count and HIV viral load assessment results.
- Record details of any nonstudy vaccinations given and antiretroviral medications taken since the last visit.
- Complete the maternal participant's source documents.
- Record AEs, AESIs, and SAEs as described in [Section 8.4](#) and [Section 10.2](#).

Note: Active elicitation and collection of AEs and SAEs through 28 days after vaccination must occur even if delivery occurs within 28 days after vaccination.

- The investigator or an authorized designee completes the CRF.
- Maternal participants or their parent(s)/legal guardian (if a minor) will be instructed to contact the site to report any significant illness (new or worsening), medically attended visit, or any hospitalization that occurs during the study period as detailed in [Section 10.2.3](#).
- Request the maternal participant or the participant's parent(s)/legal guardian (if a minor) to contact the site if she goes into labor/is admitted to the maternal unit (the study staff may contact the maternal participant prior to the next study visit to remind her, if applicable).

8.10.4. Maternal Participant: Delivery (Maternity Unit)

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

- Ensure that the maternal participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in [Section 7.2](#).
- Obtain details of any postnatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [eg, HBIG] or Rho(D) immune globulin [eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given since the last visit.
- Record details of any nonstudy vaccinations given and antiretroviral medications taken since the last visit.
- Collect a blood sample of approximately 15 mL for serologic assessments.

Note: The maternal participant's blood sample can be taken at any time during the delivery visit, **preferably before delivery**. In the event that the blood sample cannot be obtained before delivery, the sample should be collected as close to delivery as possible and at most 48 hours postpartum.

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

- Record pregnancy outcome information, including vital status of the infant (live, stillbirth, etc), mode of delivery (vaginal delivery or cesarean delivery), and the use of any assisted devices (forceps or vacuum).
- Record standard-of-care CD4 count and HIV viral load assessment results taken during delivery.

Note: If the CD4 count and HIV viral load assessment is not performed as part of the participant's routine medical care at delivery, a local laboratory assessment should be performed and the results recorded in the CRF.

- If the participant did not have the 1-month postvaccination follow-up visit, review the participant's e-diary data and record assessment in the CRF. Assess compliance and collect stop dates for any local reaction or systemic event ongoing since the 7-day follow-up period after vaccination. Document in the CRF.

- For any ongoing local reactions or systemic events, the site will follow up until resolution and document and record stop dates in the CRF.
- Collect the sponsor-provisioned e-diary/assist the participant with removing the e-diary study application from personal device.
- Ensure that all data have been transferred before deactivating the e-diary or deleting the application.
- Remind maternal participants or the participant's parent(s)/legal guardian (if a minor) that the study staff may contact them to obtain additional information on events entered into the e-diary until they resolve.
- Record AEs, AESIs, and SAEs as described in [Section 8.4](#) and [Section 10.2](#).
- Ask the maternal participants or the participant's parent(s)/legal guardian (if a minor) to contact the site to report any significant illness (new or worsening), medically attended visit, or any hospitalization that occurs during the study period as detailed in [Section 10.2.3](#).
- Ask the maternal participant and the participant's parent(s)/legal guardian (if a minor) to contact the site staff or investigator if the participant's newborn infant experiences any significant illness (new or worsening), medically attended visit, or any hospitalization that occurs during the study period as detailed in [Section 10.2.3](#).
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.5. Maternal Participant: 6-Month Postdelivery Visit (Clinic, Home, or Telephone; 180 to 210 Days After Delivery)

- Obtain details of any postnatal steroid treatment, Ig (including monoclonal antibodies or immune globulin [eg, HBIG] or Rho(D) immune globulin [eg, RhoGAM]), or blood products (eg, whole blood, packed cells) given since the last visit.
- If available, record standard-of-care CD4 count and HIV viral load assessment results.
- Record details of any nonstudy vaccinations given and antiretroviral medications taken since the last visit.
- Ensure all local reactions and systemic events entered into the e-diary have a resolve date noted.
- Record AEs, AESIs, and SAEs as described in [Section 8.4](#) and [Section 10.2](#).

- Complete the maternal participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.10.6. Maternal Participant: Unscheduled Reactogenicity Visits

If the maternal participant or the participant's parent(s)/legal guardian (if a minor) reports 1 or more of the following, a contact **must** occur as soon as possible between the maternal participant and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled reactogenicity visit is required. Based on local practice in certain countries/locales, maternal participants may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns regarding reactogenicity events, including:

- Redness at the injection site on the arm in which the study intervention was administered measuring >20 measuring device units (>10.0 cm);
- Swelling at the injection site on the arm in which the study intervention was administered measuring >20 measuring device units (>10.0 cm);
- Severe injection site pain on the arm that the study intervention was administered;
- Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$); or
- Any severe systemic event.

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

- The maternal participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator or an appropriate designee determines that the visit is not required.

Note: All contact must be recorded in the maternal participant's source notes and in the CRF.

Any ongoing reactions must be assessed until resolved prior to or at the next scheduled visit.

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

- Measure oral temperature.

- Measure the participant's heart rate.
- Measure the participant's blood pressure (seated).
- Measure the minimum and maximum diameters of redness (if present) on the arm in which the study intervention was administered.
- Measure the minimum and maximum diameters of swelling (if present) on the arm in which the study intervention was administered.
- Assess if necrosis is present at the injection site on the arm in which the study intervention was administered.
- Assess if any exfoliative dermatitis is present.
- Assess any injection site pain on the arm in which the study intervention was administered that is present in accordance with the reactogenicity grading scale provided in [Section 8.3.4.1](#).
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in [Section 8.3.4.2](#).

Note: For severe pain at the injection site resulting in an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, any necrosis on the arm in which the study intervention was administered, or exfoliative dermatitis, the investigator or qualified designee must assess these events.

- Ask the participant or the participant's parent(s)/legal guardian (if a minor) if she attended an emergency room visit, had a medically attended visit, or was hospitalized.
- Record AEs, AESIs, and SAEs as described in [Section 8.4](#) and [Section 10.2](#).
- Complete the participant's source documents.
- The investigator or an authorized designee will complete the CRFs.
- The study staff may contact the participant to obtain additional information on events entered into the e-diary, as appropriate.

8.11. Procedures – Infant Participants

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

- Assign a single infant participant identifier. This will be assigned manually by the site using the following convention: the infant participant's identifier will be the maternal participant's IRT-generated numeric ID but with the fifth digit changed to a 2 (eg, if the maternal participant is given number 10011001, then the infant will be 10012001).
- Ensure that a cord blood sample of approximately 10 mL for immunogenicity assessments has been collected. Cord blood is collected from the umbilical cord vein attached to the placenta prior to the blood clotting within the cord and after the umbilical cord has been clamped and cut. This sample should be labeled with the infant's participant ID number. If cord blood is unavailable, a peripheral blood sample may be collected from the infant participant preferably within 24 hours, but up to 7 days, after birth. The volume of blood collected will be based on the weight of the infant (refer to [Table 1](#)).
- Ensure and document that all the infant inclusion criteria and none of the infant exclusion criteria are met.
- Collect demography (including date of birth, sex, race, and ethnicity). The date of birth (as permitted by local regulations) will be collected to critically address efficacy analyses and evaluate the immune response and safety profile by age.
- Obtain and record the infant's length, head circumference, and weight at birth.
- Obtain and record the infant's birth data, including GA and Apgar score.
- Obtain and record details of childcare/daycare (for infant participants).
- Obtain and record details of breastfeeding information (including whether or not the maternal participant is breastfeeding exclusively).
- Measure vital signs, including temperature, heart rate, and respiratory rate.
 - Standard-of-care vital signs and examination procedures can be considered for use in the study, provided they were performed within 72 hours after birth. Note: Please reference the physical examination procedures below for details.
- Perform a physical examination, noting any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; back; musculoskeletal; extremities; genitourinary; neurological; and lymph nodes if not performed as part of standard of care.

- Abnormal results must be recorded on source documents as well as the physical examination pages of the CRF only if the abnormal findings are deemed to be clinically significant; these results should be recorded on the AE pages of the CRF.
- Record details of any congenital anomalies on the AE page of the CRF, and report as an SAE as described in [Section 10.2](#).
- Record results of any standard-of-care HIV testing performed.
- Record any medication as described in [Section 6.9.4.1](#).
- Obtain details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given to the infant participant since birth.
- Record AEs, NDCMCs, AESIs, and SAEs as described in [Section 8.3](#) and [Section 10.2](#).
- Remind the participant's parent(s)/legal guardian, as appropriate, to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.11.2. Infant Participants: Visit 2 – 1-Month Follow-Up (Clinic or Home; 28 to 48 Days After Birth)

- Obtain and record details of childcare/daycare (for infant participants).
- Obtain and record details of breastfeeding information (including whether or not the maternal participant is breastfeeding exclusively).
- Obtain and record the infant's length, head circumference, and weight.
- Measure vital signs, including temperature, heart rate, and respiratory rate.

Note: Standard-of-care measurement procedures can be considered for use at this study visit if they were performed within the window of the study visit.

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

Note: Standard-of-care examination procedures can be considered for use at this study visit if they were performed within the window of the study visit.

- Record results of any standard-of-care HIV testing performed to confirm HIV status.
- Record any medication as described in [Section 6.9.4.1](#).
- Record details of any newly emergent congenital anomalies on the AE page of the CRF, and report as an SAE as described in [Section 10.2](#).
- Record AEs, NDCMCs, AESIs, and SAEs as described in [Section 8.3](#) and [Section 10.2](#).
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Remind the participants' parent/legal guardian, as appropriate, to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.11.3. Infant Participants: Visit 3 – 6-Month Follow-Up Visit (Telephone, Clinic, or Home; 180 to 210 Days After Birth)

- Obtain and record details of childcare/daycare (for infant participants).
- Obtain and record details of breastfeeding information (including whether or not the maternal participant is breastfeeding exclusively).
- If a clinic or home visit is performed, obtain and record the infant's vital signs (temperature, heart rate, and respiratory rate), length, head circumference, and weight. Note: Standard-of-care measurement procedures can be considered for use at this study visit if they were performed within the window of the study visit.
- If a clinic or home visit is performed, perform a targeted physical examination, if not performed as part of standard of care, noting any clinically significant abnormalities in the source documents. Newly identified abnormal findings must be recorded on source documents and, if considered clinically significant in the judgment of the investigator/examiner, on the AE page of the CRF.

Note: Standard-of-care examination procedures can be considered for use at this study visit if they were performed within the window of the study visit.

- Record details of any newly emergent congenital anomalies on the AE page of the CRF, and report as an SAE as described in [Section 10.2](#).
- Record results of any standard-of-care HIV testing performed to confirm HIV status.
- Record any medication as described in [Section 6.9.4.1](#).
- Record AEs, NDCMCs, AESIs, and SAEs as described in [Section 8.3](#) and [Section 10.2](#).
- Obtain and record details of any Ig (including monoclonal antibodies [eg, Synagis] or immune globulin [eg, HBIG]) or blood products (eg, whole blood, packed cells) given since the last visit.
- Complete the infant participant's source documents.
- The investigator or an authorized designee completes the CRF.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in the 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. Statistical Hypothesis/Hypotheses

There are no statistical hypotheses for this descriptive study.

9.1.1. Estimands – Maternal Participants

9.1.1.1. Safety

In maternal participants receiving 1 dose of the study intervention:

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

9.1.1.2. Immunogenicity

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

- The immune response, estimated by the GMT for RSV A and RSV B serum NTs.
- The immune response, estimated by the GMFR from baseline in RSV A and RSV B serum NTs.
- GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs of the RSV vaccine group to the placebo group.

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

9.1.2. Estimands – Infant Participants

9.1.2.1. Safety

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

- The percentage of infant participants with specific birth outcomes.
- The percentage of infant participants having AEs from birth through 1 month of age.
- The percentage of infant participants having SAEs and NDCMCs from birth through 6 months of age.

9.1.2.2. Immunogenicity

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

- Functional antibody levels estimated by the GMT for RSV A and RSV B serum NTs.
- GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs of the RSV vaccine group to the placebo group.

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

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

9.1.3. Multiplicity Adjustment

There is no multiplicity adjustment for the study, as the study is descriptive in nature.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity – maternal	All maternal participants who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
Evaluable immunogenicity – infant	All infant participants who are eligible, are born to the maternal participants who received the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
mITT – maternal	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.
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 participants who receive at least 1 dose of the study intervention.
Safety – infant	All infant participants who are born to vaccinated maternal participants.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe 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.

9.3.1. General Considerations

Unless stated otherwise, “vaccine group” in this section refers to participants receiving RSVpreF or placebo. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing AE dates will be imputed according to Pfizer safety rules. Completely missing e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT population if there is a large enough difference in sample size between the mITT population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group (RSVpreF or placebo) to which they were randomized.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%) and the numerator (n) and the denominator (N) used in the percentage calculation. The 95% CI for percentage, and for difference in percentages, may also be presented where appropriate. The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson). The 95% CI for the difference in the proportions will be computed using the Miettinen and Nurminen method. The 95% CI will be presented in terms of percentage.

9.3.1.2. Analyses for Continuous Data

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

9.3.1.2.1. Geometric Means

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. Geometric means and associated 2-sided 95% CIs will be derived by calculating group means and CIs on the natural log scale based on the Student t distribution, and then exponentiating the results.

9.3.1.2.2. Geometric Mean Fold Rises

GMFRs will be calculated as the group mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. GMFRs are limited to participants with nonmissing values at both time points. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. Geometric Mean Ratios

GMRs will be calculated as the mean of the difference of logarithmically transformed assay results from participants who received RSVpreF and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

9.3.2.1. Primary Endpoint Analyses – Maternal Participants

Endpoint	Statistical Analysis Methods
Safety	- Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Prespecified local reactions (pain at the injection site, redness, and swelling) and prespecified systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) from Day 1 through Day 7 after vaccination will be presented by maximum severity and any severity. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CI (Section 9.3.1.1). - AEs and SAEs will be categorized according to MedDRA terms. All AEs within 1 month from vaccination and SAEs throughout the study will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CIs for each vaccine group (Section 9.3.1.1). - A 3-tier approach will be used to summarize AEs. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in the percentage of participants reporting the events between the RSVpreF and the placebo group will be calculated using the test statistic proposed by Miettinen and Nurminen. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. A 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. Descriptive summary statistics (counts and percentages) will be provided for Tier 3 events for each vaccine group. - The safety analyses are based on the safety population. Participants will be summarized according to the vaccine group corresponding to the study intervention they actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be addressed using the Pfizer safety rules.

9.3.2.2. Primary Endpoint Analyses – Infant Participants

Endpoint	Statistical Analysis Methods
Safety	- Specific birth outcomes will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CIs. - AEs and SAEs will be categorized according to MedDRA terms. All AEs from birth through 1 month of age and SAEs/NDCMCs from birth through 6 months of age will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CIs (Section 9.3.1.1). - A 3-tier approach will be used to summarize AEs.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

9.3.3.1. Secondary Endpoint Analyses – Maternal Participants

Endpoint	Statistical Analysis Methods
Immunogenicity	- GMT of the RSV A and RSV B serum NTs at each available time point, by vaccine group. - GMT of the combined RSV A/B serum NT, defined as the geometric mean of the RSV A and RSV B serum NTs, at each available time point, by vaccine group. - GMFR for RSV A and RSV B serum NTs from before vaccination to each available time point after vaccination, by vaccine group. - GMFR of the combined RSV A/B serum NT, defined as the geometric mean of the RSV A and RSV B serum NTs, from before vaccination to each available time point after vaccination, by vaccine group.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

9.3.4.1. Exploratory Endpoint Analyses – Maternal Participants

Endpoint	Statistical Analysis Methods
Immunogenicity	GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs at delivery from maternal participants living with HIV of this study compared to non-HIV-infected maternal participants from Study C3671008. The GMR will be estimated from an analysis of covariance model, including adjustment for time from vaccination to delivery, and may include other covariates. As GMT at delivery varies, a comparison will occur based on matching geographic locations using the Study C3671008 participants. The GMRs at delivery after vaccination will be provided along with associated 2-sided 95% CIs.

Endpoint	Statistical Analysis Methods
	Immunobridging success will be declared if the lower bound of the 2-sided 95% CI for the GMR is >0.5.

9.3.4.2. Exploratory Endpoint Analyses – Infant Participants

Endpoint	Statistical Analysis Methods
Immunogenicity	- GMT of the RSV A and RSV B serum NTs at birth, by vaccine group. - GMT of the combined RSV A/B serum NT, defined as the geometric mean of the RSV A and RSV B serum NTs at birth, by vaccine group.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. The analysis will be performed after all participants completed the study and when all of the data are available.

9.5. Sample Size Determination

The study will randomize approximately 330 maternal participants (randomization ratio 1:1 so that 165 receive active vaccine and 165 receive placebo). The total sample size is not based on any statistical hypothesis testing.

For safety outcomes in the study, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE with 165 participants in each vaccine group.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rate

Sample Size	Assumed True Rate of an AE	Probability of Observing at Least 1 AE
165	1%	81.0%
	2%	96.4%
	3%	99.3%
	4%	99.9%
	5%	>99.9%
	6%	>99.9%
	10%	>99.9%
	12%	>99.9%

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH GCP guidelines, the IRB/EC, European Regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, 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 study intervention, 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 the ICH GCP guidelines 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 – Maternal Participant

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the maternal participant and the participant's parent(s)/legal guardian (if a minor) and answer all questions regarding the study. The participant and the participant's parent(s)/legal guardian (if a minor) should be given sufficient time and opportunity to ask questions and to decide whether to participate in the trial.

Maternal participants must be informed that their participation is voluntary, and that the participation of their infants once born is voluntary. Maternal participants and the participant's parent(s)/legal guardian (if a minor) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each maternal participant and the participant's parent(s)/legal guardian (if a minor) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The maternal participant and the participant's parent(s)/legal guardian (if a minor) must be informed that their 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 maternal participant and the participant's parent(s)/legal guardian (if a minor).

The maternal participant and the participant's parent(s)/legal guardian (if a minor) must be informed that their 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 maternal study participant and the participant's parent(s)/legal guardian (if a minor) is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

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

Maternal participants or their parent(s)/legal guardian (if a minor) must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the maternal participant or the participant's parent(s)/legal guardian (if a minor).

Maternal participants who are rescreened are required to sign a new ICD.

If, during the study, the investigator determines that the maternal participant is for any reason no longer capable of providing informed consent, the infant's continued participation in the study requires consent to be obtained from the parent(s)/legal guardian as determined by local regulations, legal requirements, and the IRB/EC.

Informed Consent: Infant Participant

Before any study-specific activity is performed, the investigator, or a person designated by the investigator, will obtain written informed consent from each maternal participant and the participant's parent(s)/legal guardian (if a minor). This will include written informed consent for the mother and the fetus during the pregnancy, and the infant's continuation in the study after birth.

The maternal ICD will include consent for obtaining blood from the umbilical cord.

Note: For the infant participant, the term parent(s)/legal guardian denotes the "legally authorized representative."

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

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 will 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 participants 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an EDMC. The EDMC is independent of the study team and includes only external members. The EDMC charter describes the role of the EDMC in more detail.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.6. 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 EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs, including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on a 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and 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, including definition of study-critical data items and processes (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, virtual, or onsite monitoring), are provided in the data management and monitoring plan and maintained and utilized by the sponsor or designee.

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

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.

10.1.8. Source Documents

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

Data reported on the CRF or entered in the eCRF that are 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 a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records for SAE reporting may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).
- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).
- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 sponsor or designee/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 the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/ECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

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.

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after the PCD or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, “publication”) before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention– or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor’s Medically Qualified Individual

The contact information for the sponsor’s MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor’s MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) the participant’s study identification number, (c) the site emergency phone number active 24 hours/day, 7 days per week, and (d) the Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

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

10.2.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE: ○ Is associated with accompanying symptoms. ○ Requires additional diagnostic testing or medical/surgical intervention. ○ Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition. • New condition 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 the study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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Events **NOT** Meeting the AE Definition

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

10.2.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

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 admitted (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.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

d. Results in persistent or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

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

10.2.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs via the PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the PSSA 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 PSSA for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the PSSA to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* Notification of EDP alone (not associated with an AE or SAE) is not required when the study population is pregnant women. However, if the mother or the fetus experiences any SAE, the information is reported to Pfizer Safety All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety via the PSSA.

** **EDB** is reported to Pfizer Safety via the PSSA, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via the PSSA.

- When an AE or 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 or 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 AE or 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. Refer to [Section 10.1.9](#) for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- 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 or 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:

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- **Severe:** A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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 the study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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 study intervention caused the event, then the event will be handled as “related to study intervention” 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 PSSA 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 HCPs.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken offline 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 DCT has been taken offline, 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 the Vaccine SAE Report Form

- Facsimile transmission of the Vaccine SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine 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 Vaccine SAE Report Form pages within the designated reporting time frames.

10.2.5. Newly Diagnosed Chronic Medical Conditions

An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects (eg, asthma).

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

Potential Cases of Drug-Induced Liver Injury

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

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 AST and/or ALT precede T bili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values $\geq 3 \times \text{ULN}$ AND a T bili value $\geq 2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $< 2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** T bili 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 $\geq 3 \times \text{ULN}$; or $\geq 8 \times \text{ULN}$ (whichever is smaller).

- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of $\geq 1 \times \text{ULN}$ **or** if the value reaches $\geq 3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), 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/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation as defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.4. Appendix 4: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see [Section 6.1.2](#) for the list of sponsor medical devices).

10.4.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Section 10.2.1. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.4.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Section 10.2.2.
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition

- A USADE (also identified as UADE in US Regulation 21 CFR 813.3) is an SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.4.3. Definition of Device Deficiency

Device Deficiency Definition

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.4.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording

- When a device deficiency occurs, it is the responsibility of the investigator or designee to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator or designee will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice.
- If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.
- The investigator or designee will notify the sponsor study team by contact method (eg, telephone, email) within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.
- The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group.
- If the investigator or designee determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator or designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details related

Device Deficiency Recording

to the role of the device in regard to the SAE must be included in the Medical Device Constituent Supplemental Form as outlined in [Section 8.4.1.1](#) and [8.4.1.2](#).

- 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. Refer to [Section 10.1.9](#) for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- For device deficiencies, it is very important that the investigator or designee describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have 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.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency

- Follow-up applies to all participants, including those who discontinue study intervention.
- 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 device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the sponsor study team.
- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Medical Device Constituent Supplemental Form within 24 hours of receipt of the information, according to the requirements provided in [Section 10.2](#).

10.5. Appendix 5: Abbreviations

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

Abbreviation	Term
AE	adverse event
ADE	adverse device effect
ADL	activity/activities of daily living
AESI	adverse event of special interest
Al(OH) ³	aluminum hydroxide
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
ART	antiretroviral therapy
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BMI	body mass index
CFR	Code of Federal Regulations (United States)
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CpG	cytosine phosphate guanine
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDD	estimated delivery date
e-diary	electronic diary

Abbreviation	Term
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
EU-SmPC	summary of product characteristics (European Union)
FDA	Food and Drug Administration (United States)
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine
GA	gestational age
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HCP	healthcare provider
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
Ig	immunoglobulin
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP	internet protocol
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
IUI	intrauterine insemination
IV	intravenous
LBW	low birth weight
LFT	liver function test
LMP	last menstrual period

Abbreviation	Term
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
MA-LRTI	medically attended lower respiratory tract illness
MCAR	missing completely at random
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MQI	medically qualified individual
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NT	neutralizing titer
PCD	primary completion date
PCR	polymerase chain reaction
PFS	prefilled syringe
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
T bili	total bilirubin
Tdap	tetanus, diphtheria, and acellular pertussis vaccine
Th2	T-helper type 2
UADE	unanticipated adverse device event
ULN	upper limit of normal
US; USA	United States

Abbreviation	Term
USADE	unanticipated serious adverse device effect
USPI	United States prescribing information
VE	vaccine efficacy

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