A PHASE 1, OPEN-LABEL, AGE-DESCENDING, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS PREFUSION F SUBUNIT VACCINE (RSVpreF) IN CHILDREN 2 TO <18 YEARS OF AGE

Study Intervention Number:	PF-06928316
Study Intervention Name:	Respiratory Syncytial Virus (RSV) Vaccine
US IND Number:	017931
EU CT Number:	2022-503134-32-00
ClinicalTrials.gov ID:	NCT05900154
Pediatric Investigational Plan Number:	EMEA-002795-PIP02-21
Protocol Number:	C3671016
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Phase 1 Study of the Safety, Tolerability, and Immunogenicity of RSVpreF in Children 2 to <18 Years of Age

Document History

Document	Version Date
Amendment 1	09 Feb 2024
Original protocol	31 Jan 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (09 Feb 2024)

Overall Rationale for the Amendment:

This amendment is made to address a CBER recommendation to amend the protocol design to be consistent with an early-phase clinical study.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Added the clinicaltrials.gov reference and sponsor legal address to the title page.	To reflect the trial posting to clinicaltrials.gov.	Title page
Removed Phase 2/3 content.	To address CBER feedback.	Throughout protocol
Nonsubstantial Modification(s)		
Updated the text with respect to the FDA approval of RSVpreF (Abrysvo®) for marketing in individuals 60 years of age and older and pregnant individuals at 32-36 weeks of gestational age in the US and to approvals of prophylactic monoclonal antibodies for RSV.	To provide updated information on approvals for the RSV vaccine and monoclonal antibodies.	Section 1.1 Section 2 Section 11
Updated safety profile and risk assessment information.	To reflect current safety data regarding RSVpreF.	Section 2.1 Section 2.3.1
Deleted potential risk from risk assessment.	The global SARS-CoV-2 pandemic has ended per WHO and risk is no longer applicable.	Section 2.3.1
Updated the order of the prevaccination RSV serostatus procedure.	Updated per PACL.	Section 1.3.1. Section 8.10.1 where applicable
Added AESI surveillance through the end of study participation.	Updated per PACL #3.	Section 1.1 Section 1.3 Section 8.4.1 Section 8.4.8 Section 8.10 where applicable

Description of Change	Brief Rationale	Section # and Name
Updated the text to provide more clarity regarding the analysis of partially missing e-diary data.	To add clarification.	Section 9.3.1 Section 9.4.1
Updated section to ensure compliance with current external regulations and internal policies.	To ensure the protocol is compliant with current external regulations and internal policies.	Section 10.1.3 Section 10.1.3.1 Section 10.1.3.2 Section 10.1.6 Section 10.1.7 Section 10.1.8 Section 10.1.9 Section 10.1.10
Made minor editorial changes.	To align with amendment and template updates and/or to improve clarity and navigation throughout the document for sites.	All

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, Age-Descending, Dose-Finding Study to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus Prefusion F Subunit Vaccine (RSVpreF) in Children 2 to <18 Years of Age

Brief Title:

A Phase 1 Study of the Safety, Tolerability, and Immunogenicity of RSVpreF in Children 2 to <18 Years of Age

Regulatory Agency Identification Number(s):

US IND Number:	017931
EU CT Number:	2022-503134-32-00
ClinicalTrials.gov ID:	NCT05900154
Pediatric Investigational Plan Number:	EMEA-002795-PIP02-21
Protocol Number:	C3671016
Phase:	1

Rationale:

RSV is the leading cause of LRTI among infants and young children globally.

Pfizer is developing a vaccine to protect against RSV disease. The vaccine, RSVpreF, contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. On 31 May 2023 and 21 Aug 2023, the FDA approved RSVpreF (Abrysvo®) for marketing in individuals 60 years of age and older and in pregnant individuals, respectively. On 23 Aug 2023, the European Commission granted marketing authorization for RSVpreF to help protect infants through maternal immunization and to protect older adults. Additional applications are under review by other regulatory agencies around the world.

This proposed pediatric Phase 1 study (C3671016) will evaluate different dose levels of RSVpreF in children 2 to <18 years of age to identify the dose level for Phase 2/3 trials in this age cohort. In this study, children will be considered high risk if they are 5 to <18 years of age and have certain chronic medical conditions, or if they are 2 to <5 years of age and are healthy or have certain medical conditions. Children 2 to <5 years of age are considered at high risk of increased morbidity due to RSV infection based on their age alone.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability of RSVpreF at each dose level in children 5 to <18 years of age and children 2 to <5 years of age.	Prompted local reactions (pain at the injection site, redness, and swelling). Prompted systemic events (fever, vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain). AEs. SAEs. NDCMCs.	In participants receiving 1 dose of study intervention at each dose level, for each age stratum: • The percentage of participants reporting local reactions within 7 days after vaccination. • The percentage of participants reporting systemic events within 7 days after vaccination. • The percentage of participants reporting AEs from vaccination through 1 month after vaccination. • The percentage of participants reporting SAEs throughout the study. • The percentage of participants reporting NDCMCs throughout the study.
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by RSVpreF at each dose level in children 5 to <18 years of age and children 2 to <5 years of age.	RSV A and RSV B NTs.	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • GMTs of NT for RSV A and RSV B 1 month after vaccination. • GMTs of NT for RSV A and RSV B before vaccination. • GMFRs of NT for RSV A and RSV B from before vaccination to 1 month after vaccination.
To describe the cell-mediated immune response in children 5 to <18 years of age and children 2 to <5 years of age.	RSV F antigen–specific CD4+ T cells secreting IFNγ. RSV F antigen–specific CD4+ T cells secreting IL-4.	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • Median frequencies of RSV F antigen–specific CD4+ T cells expressing IFNγ before vaccination and 1 month after vaccination. • Median frequencies of RSV F antigen–specific CD4+ T cells expressing IL-4 before vaccination and 1 month after vaccination.

Overall Design:

This is a Phase 1, open-label, age-descending, dose-finding study of the safety, tolerability, and immunogenicity of RSVpreF in RSV-seropositive children 2 to <18 years of age. Participants will be divided into 2 age strata: 5 to <18 years and 2 to <5 years. All participants will receive 1 dose of RSVpreF.

A single dose of RSVpreF 120 µg will be administered to the older age stratum first. Upon confirmation of an acceptable safety profile by the IRC, dose administration will proceed in the 2- to <5-year age stratum with 60 µg. Pending IRC approval, the younger age stratum will receive a single 120-µg dose of the vaccine. The older age stratum may also receive a single dose of RSVpreF 60 µg. Stopping rules will apply.

Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added at levels below the lowest stated dose.

All participants in the 2- to <5-year age stratum will require a blood sample to assess RSV serostatus during the screening visit, and only those who are seropositive will be administered RSVpreF on Day 1. All participants 5 years of age and older will be considered RSV seropositive and will not require a screening test.

Participants will have a baseline blood draw prior to vaccination on Day 1 and a postdose blood draw 1 month after vaccination to assess immunogenicity.

Additional blood will be required for PBMC isolation and will be collected simultaneously with the immunogenicity sample, both on Day 1 and again 1 month after vaccination. Frequencies of RSV F antigen–specific CD4+ T cells secreting specific cytokines will be measured both before and after vaccination.

The study duration for each participant will be approximately 6 months.

Internal Review Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRC charter describes in detail the roles of the IRC members.

Number of Participants:

This is an open-label dose-finding study. A single dose of RSVpreF 120 µg will be given to approximately 40 participants in the 5- to <18-year age stratum first, equally divided between healthy children and those with high-risk chronic medical conditions. Upon IRC approval, a dose of 60 µg will be given to 20 participants in the 2- to <5-year age stratum. If, per the IRC, 60 µg is determined to be safe and tolerable, another 20 participants in the 2- to <5-year age stratum will receive the 120-µg dose. The IRC may also request that a single dose of RSVpreF 60 µg be given to approximately 40 participants in the 5- to <18-year age stratum.

Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added at levels below the lowest stated dose. Approximately 60 to 120 participants are expected to be enrolled.

Age Stratum (Years)	Number of Participants
2 to <5	~20/~20[a]
5 to <18	~40/~40[a,b]
Total	~60-120

a. Up to 2 dose levels of RSVpreF (120 µg and 60 µg) will be tested in participants.
b. Approximately 40 participants 5 to <18 years old will be enrolled, with ~20 healthy participants and ~20 participants with high-risk chronic medical conditions receiving each dose level.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment in the study:

Age and Sex:

1. Participants 2 to <18 years of age at enrollment (signing of the ICD or providing assent to participate) at Visit 1.

Disease Characteristics:

2. Participants 2 to <18 years of age should either be healthy or be considered by the investigator to be at high risk of RSV disease based on the presence of 1 of the following chronic medical conditions:

    - Cystic fibrosis
    - Medically treated asthma
    - Other chronic respiratory diseases and malformations of the lung
    - Down syndrome
    - Neuromuscular disease
    - Cerebral palsy

- Hemodynamically significant or symptomatic congenital heart disease

Details of the chronic medical conditions listed above are further defined in the investigator site file.

Other Inclusion Criteria:

1. All participants 2 to <5 years of age must be seropositive for RSV as confirmed by serology.

2. Participants' parent(s)/legal guardian(s) and participants, as age appropriate, who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, and other study procedures,. Participants' parent(s)/legal guardian(s) should be available for telephone contact with site staff for the duration of the study.

3. The participant's parent(s)/legal guardian is capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).

Exclusion Criteria

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

Medical Conditions:

1. Immunocompromised individuals associated with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

2. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus. Note: Stable type 1 diabetes and hypothyroidism are permitted.

3. Other 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.

4. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

6. Individuals with a history of epilepsy or other seizure disorders, or a history of seizures and/or other neurological complications following vaccination.

Prior/Concomitant Therapy:

7. Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation. Children who may have been exposed to investigational RSV vaccines through maternal immunization will be permitted.

8. Receipt of investigational or approved monoclonal antibodies against RSV within 6 months before study intervention administration, or planned receipt throughout the study.

9. Receipt of blood/plasma products or immunoglobulins within 28 days before study intervention administration, or planned receipt throughout the study.

10. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before study intervention administration, or planned receipt throughout the study.

    Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease). Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving study intervention within 28 days prior to study entry and/or for the duration of study participation.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

12. 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.

Study Arms and Duration:

Study Arms and Study Interventions

Intervention Name	PF-06928316 (RSVpreF)
Arm Name (group of participants receiving a specific vaccine or no vaccine)	Active vaccine group
Unit Dose Strength(s)	120 µg and/or 60 µg
Type	Vaccine
Route of Administration	Intramuscular
Use	Experimental
IMP or NIMP/AxMP	IMP

Dose finding will begin at 120 µg of RSVpreF in participants 5 to <18 years of age. The IRC will review safety data (e-diary and AEs) acquired up to 7 days after vaccination once a minimum of 10 and up to approximately 40 participants have been vaccinated. Upon IRC confirmation of an acceptable safety profile in the 5- to <18-year-olds, dose administration may commence at 60 µg of RSVpreF in participants 2 to <5 years of age. The same process will be followed before vaccinating with 120 µg of RSVpreF in the 2- to <5-year-olds. Upon IRC review, RSVpreF 60 µg may be given to participants in the 5- to <18-year age stratum.

Study Duration:

The study duration for each participant will be approximately 6 months.

Statistical Methods:

This Phase 1 study is descriptive; thus, sample size is not based on any statistical criteria. Safety and immunogenicity data will be descriptively summarized for this cohort, and immunogenicity data in this cohort may be descriptively compared with other study results.

Ethical Considerations:

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF support a favorable benefit/risk profile. Anticipated AEs after vaccination are expected to be similar to those observed following vaccination with the same vaccines (mild to moderate reactogenicity), which are manageable using routine symptom-driven standard of care.

Because of the history of vaccine-mediated ERD following immunization of RSV-naïve infants in the 1960s with an FI-RSV vaccine, this study will be limited to seropositive children only and will assess the cellular response (Th1/Th2 balance) to RSVpreF. Th1- and Th2-specific cytokines will be used as a surrogate to characterize the cellular immune response and predisposition to enhanced disease. Unlike the FI-RSV vaccine, RSVpreF is an F glycoprotein subunit stabilized in the prefusion conformation, elicits 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 mothers. Available evidence indicates that RSVpreF is efficacious and is unlikely to confer any risk of enhanced disease.

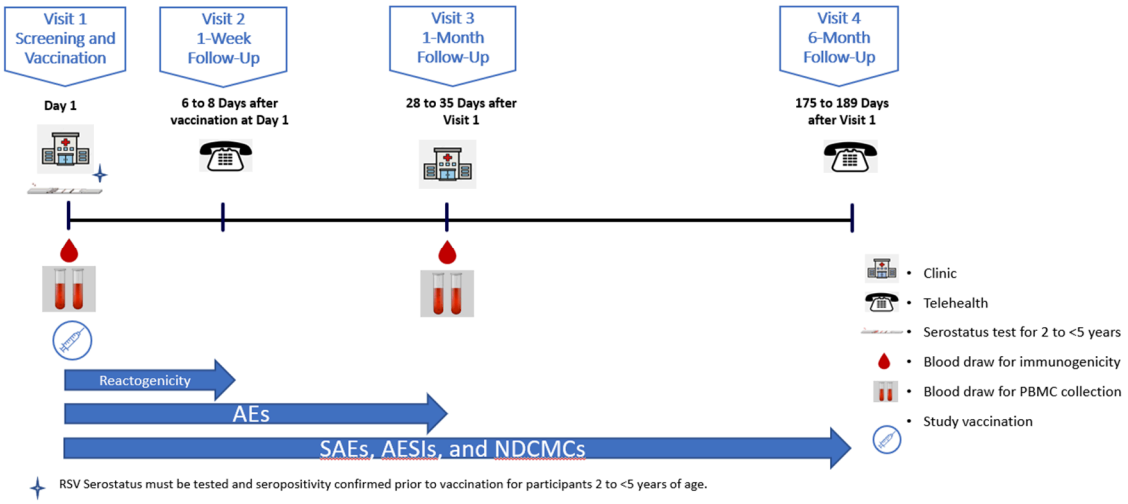
The expected safety profile of this vaccine therefore supports initiation of this clinical study.

- Based on the experience with RSVpreF, the potential risks are:
    - Local reactions and systemic events such as injection site redness, injection site swelling, and injection site pain; and fever, fatigue/tiredness, headache, muscle pain, and joint pain.
    - Guillain-Barré syndrome. In Study C3671013, conducted in adults 60 years of age and older, there were 2 cases of Guillain-Barré syndrome or its variants identified with a plausible temporal relationship with vaccination among >18,000 individuals who received RSVpreF. Both cases had confounding factors or alternative etiology.
    - Other events of special interest include atrial fibrillation, polyneuropathy, preterm birth (delivery at <37 0/7 weeks' gestation), and hypertensive disorders of pregnancy.
    - Theoretical risk for RSV vaccine–elicited ERD.
- The study procedure-related risks include:
    - Venipuncture will be performed during the study.

1.2. Schema

5- to <18-Year Age Stratum		2- to <5-Year Age Stratum
Phase 1 All participants receive RSVpreF		**Phase 1** All participants receive RSVpreF
120 µg (n=40)	IRC[a] →	**60 µg (n=20)**
↓ IRC[b]		↓ IRC[b]
60 µg (n=40)	←	**120 µg (n=20)**
↓ IRC[c]		↓ IRC[c]
RSVpreF dose level selected		RSVpreF dose level selected

a. Progression of the study to the younger age stratum will occur upon confirmation of an acceptable safety assessment of data accumulated up to 7 days after vaccination at the 120-µg level, once a minimum of 10 and up to approximately 40 participants have been vaccinated in participants from the 5- to <18-year age stratum.
b. In each age stratum, based on safety assessment of data accumulated up to 7 days after vaccination, the IRC may request a different dose level of RSVpreF to be tested.
c. The IRC will choose a dose level for each age stratum depending on safety, tolerability, and immunogenicity data accumulated from 7 days after dose administration in each age stratum.



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.

Visit Number Abbreviations used in this table may be found in Appendix 7.	**1**	**2**	**3**	**4**	**Notes**
Visit Description	**Screening and Vaccination**	**1-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Window (Days)	**Day 1**	**6 to 8 Days After Vaccination Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day relative to start of study intervention administration (Day 1).**
Type of Visit	**Clinic**	**Telehealth**	**Clinic**	**Telehealth**	
Obtain informed consent and assent (if applicable)	X				Informed consent should be obtained prior to undergoing any study-specific procedures. See Section 10.1.3 for additional information.
Assign participant number	X				
Obtain demography and significant medical history data	X				

Visit Number Abbreviations used in this table may be found in Appendix 7.	**1**	**2**	**3**	**4**	**Notes**
Visit Description	**Screening and Vaccination**	**1-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Window (Days)	**Day 1**	**6 to 8 Days After Vaccination Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day relative to start of study intervention administration (Day 1).**
Type of Visit	**Clinic**	**Telehealth**	**Clinic**	**Telehealth**	
Perform physical examination (including height and weight)	X				Physical examinations to be completed before administration of study intervention.
Measure prevaccination temperature	X				If the temperature is >38°C (100.4°F), vaccination delay criteria apply. See Section 5.5.
Collect nonstudy vaccine information	X	X	X	X	
Collect prohibited medication use	X	X	X	X	
Confirm eligibility	X				
Review temporary delay criteria	X				
Collect blood sample for immunogenicity	~5 mL for children <10 years of age and ~10 mL for children 10 to <18 years of age		~5 mL for children <10 years of age and ~10 mL for children 10 to <18 years of age		Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.4.1).
Collect blood sample for PBMC isolation	Up to 1 mL per year of age, but no more than 10 mL		Up to 1 mL per year of age, but no more than 10 mL		Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.4.1).

Visit Number Abbreviations used in this table may be found in Appendix 7.	**1**	**2**	**3**	**4**	**Notes**
Visit Description	**Screening and Vaccination**	**1-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Window (Days)	**Day 1**	**6 to 8 Days After Vaccination Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day relative to start of study intervention administration (Day 1).**
Type of Visit	**Clinic**	**Telehealth**	**Clinic**	**Telehealth**	
Perform RSV serostatus test (for children 2 to <5 years of age only).	X				RSV serostatus must be tested and seropositivity confirmed prior to vaccination (for participants 2 to <5 years of age).
Obtain randomization number and study intervention allocation	X				
Study intervention administration	X				See Section 6.1 for additional information.
Assess acute reactions for at least 30 minutes after study intervention administration	X				See Section 6.1.1 for additional information.
Provide instructions on the reactogenicity e-diary completion requirements to the participant's parent(s)/legal guardian and assist with downloading the app or issue a provisioned device, if required	X				Parent(s)/legal guardian will record reactogenicity events each evening for 7 days, starting on the day of vaccination.

Visit Number Abbreviations used in this table may be found in Appendix 7.	**1**	**2**	**3**	**4**	**Notes**
Visit Description	**Screening and Vaccination**	**1-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Visit**	
Visit Window (Days)	**Day 1**	**6 to 8 Days After Vaccination Day 1**	**28 to 35 Days After Visit 1**	**175 to 189 Days After Visit 1**	**Day relative to start of study intervention administration (Day 1).**
Type of Visit	**Clinic**	**Telehealth**	**Clinic**	**Telehealth**	
Provide thermometer and measuring device	X				See Section 8.3 for additional information.
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	Days 1 through 7				
Contact the participant if they report a severe reaction or fever in their e-diary; arrange an unscheduled visit if required	Days 1 through 7				
Review ongoing reactogenicity e-diary symptoms reported as present on the last day of the e-diary reporting period and obtain stop dates		X	X	X	Ongoing reactogenicity e-diary events must be followed up to obtain stop dates as described in Section 8.3.4.
Collect AEs as appropriate	X	X	X		See Section 8.4 for additional information.
Collect SAEs, AESIs, and NDCMCs as appropriate	X	X	X	X	See Section 8.4 for additional information.
Collect reactogenicity e-diary device, if applicable			X		

2. INTRODUCTION

RSVpreF is being investigated for the prevention of RSV disease in 2- to <5-year-old children and in 5- to <18-year-old children with high-risk chronic medical conditions.

2.1. Study Rationale

RSV is the primary viral cause of LRTI among infants and young children globally.[1] A recent review of the global RSV burden estimated that, worldwide, RSV causes 3.6 million hospitalizations each year among children under 5 years of age, most of which occur in infants.[2] However, emerging evidence suggests that RSV disease not only occurs at a high rate in infancy, but also causes medically attended illness throughout the first 5 years of life.[3,4,5,6,7,8] The burden of RSV among healthy children 5 years of age and older is less frequently studied; however, it is well established that certain underlying medical conditions, including cystic fibrosis, medically treated asthma, other chronic respiratory diseases and malformations of the lung, Down syndrome, neuromuscular disorders, cerebral palsy, and hemodynamically significant or symptomatic congenital heart disease, predispose children to increased risk of morbidity due to RSV.[6,9,10,11,12] In this study, children will be considered "high risk" of increased morbidity due to RSV if they are 5 to <18 years of age and have 1 of the aforementioned chronic medical conditions, or if they are 2 to <5 years of age and have 1 of the aforementioned chronic medical conditions or are healthy. The younger age group is considered at risk based on age alone.

Currently, there is no vaccine prophylaxis approved for use in children 2 to <18 years of age to protect against RSV disease. A prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), that binds the RSV F glycoprotein, is recommended for use only in high-risk infants, and can prevent infant RSV disease.[13,14] A newer humanized monoclonal antibody targeting the prefusion conformation of RSV F glycoprotein, nirsevimab (Beyfortus, AstraZeneca and Sanofi), was recently approved to prevent RSV LRTD in neonates and infants born during or entering their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[15]

However, antibodies that are currently licensed or in development for children <2 years of age may be impractical for older children because of the challenges around administration of an appropriate volume and the limited half-life compared to the period of risk in children up to 5 years of age. With the lack of antiviral therapies for treatment of RSV disease, the limited usefulness of monoclonal antibody prophylaxis, and the absence of a licensed vaccine to prevent RSV disease, there exists an unmet medical need for agents that can provide prophylaxis against RSV disease in children 2 to <5 years of age and children 5 to <18 years of age who are at high risk of RSV disease.

Study C3671016 is a Phase 1 study of the safety, tolerability, and immunogenicity of RSVpreF in children 2 to <18 years of age, including children 5 to <18 years of age with high-risk medical conditions.

2.2. Background

In a recent review of the global RSV burden, the annual rate of RSV-associated hospitalization for children 1 to <5 years of age in high-income countries was 1.6 per 1000.[2] Studies conducted in Europe corroborate this global review and have shown that RSV-associated hospitalization still occurs after infancy, with rates between 6.4 and 15.0 per 1000 annually among 1-year-olds and between 0.6 and 2.3 per 1000 annually among children 2 to 4 years of age.[3,4] Studies in the US and UK have shown similar ranges of RSV disease burden estimates for these age groups.[3,4,5]

In addition to the hospitalized burden of RSV among children 1 to <5 years of age, research suggests that RSV may also cause a significant outpatient burden in this age group. A population-based study conducted by the US CDC showed that when looking at all medically attended cases of RSV (ie, hospitalized and outpatient), 78% occurred in children 1 to <5 years of age. This finding highlighted that a larger burden of RSV-associated disease exists in this age group than previously thought.[7] Therefore, it is commonly considered that children in this age group are at higher risk for RSV disease. Furthermore, household studies assessing RSV transmission patterns suggest that children 1 to <5 years of age may be the primary reservoirs for RSV transmission within families. These data suggest that prevention of RSV in this age group may help indirectly protect young children who are at highest risk of hospitalization and severe disease.[16,17,18] Despite these studies, there remains a knowledge gap on the full disease burden and potential vaccine benefit for this age group.[7]

On 31 May 2023 and 21 Aug 2023, the FDA approved RSVpreF for marketing in individuals 60 years of age and older and in pregnant individuals, respectively.[19,20] On 23 Aug 2023, the European Commission granted marketing authorization for RSVpreF to help protect infants through maternal immunization and to protect older adults.[21] Additional applications are under review by other regulatory agencies around the world.

Because of the history of vaccine-mediated RSV disease enhancement following immunization of RSV-naïve infants in the 1960s with an FI-RSV,[22] this study will be limited to seropositive children only and will assess T-cell responses to RSVpreF, specifically the Th1/Th2 profile. Unlike the FI-RSV vaccine, RSVpreF is an F glycoprotein subunit stabilized in the prefusion conformation and thus elicits a high ratio of neutralizing to nonneutralizing antibodies more closely matching the profile in naturally exposed individuals where no disease enhancement has been observed. Furthermore, the vaccine has already shown efficacy in preventing LRTI and severe LRTI in older adults and severe LRTI in infants born to vaccinated mothers (refer to Section 2.2.1). Available evidence indicates that RSVpreF is efficacious and is unlikely to confer any risk of enhanced disease.

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 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. In 616 vaccinated participants in the 50- through 85-year age group, RSV 50% NT GMFRs were high across all arms of the study, ranging from 9 to 13 from before vaccination to 1 month after vaccination and from 3 to 4 from before vaccination to 12 months after vaccination for RSV A and RSV B. 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.

- Phase 1/2 study C3671002, in 250 older adults 65 through 85 years of age, studied 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.

- 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 has an acceptable safety profile.

- A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of a Respiratory Syncytial Virus 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 120 µg RSVpreF 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 has an acceptable safety profile. The study demonstrated 100% efficacy of RSVpreF against RT-PCR–confirmed symptomatic infection.

- 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.[23] On 31 May 2023, the FDA approved RSVpreF for individuals 60 years of age and older in the US.[19] On 23 August 2023, RSVpreF was also granted marketing authorization within the EU for active immunization of adults 60 years of age and older for the prevention of LRTD caused by RSV.[21]

- C3671006 is a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study nearing completion. 1407 healthy adults ≥65 years of age were randomized 1:1 to either a coadministration group or a sequential-administration group. The intention 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. The study has yet to be analyzed.

Maternal Program Studies

The maternal program includes Phase 2b and Phase 3 studies in pregnant women and a Phase 2b study in nonpregnant women.

- C3671003 is a completed Phase 2b multicenter, randomized, placebo-controlled study in up to 650 healthy pregnant women 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 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.

- C3671004 is a completed Phase 2b study of 713 healthy nonpregnant women 18 through 49 years of age. A total of 709 participants received 120 µg RSVpreF or 240 µg RSVpreF 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 RSVpreF when coadministered with Tdap, with RSV A and RSV B 50% NT GMRs of 0.97 and 0.96 at 1 month after vaccination.

- C3671008 is a completed 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 between 24 and 36 weeks' gestation received either RSVpreF 120 µg or the placebo. The study enrolled approximately 7400 pregnant individuals. Primary analysis results (data cutoff: September 2022) demonstrated a VE of 81.8% against severe MA-LRTI due to RSV in infants from birth through the first 90 days of life, with a 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.[24] Based on these data, approval of RSVpreF for the protection of infants through maternal immunization was received in the US and EU, with additional applications under review by regulatory agencies around the world.[20,21]

2.3. Benefit/Risk Assessment

RSV is the primary viral cause of LRTI among infants and young children globally.[1]

There is no approved direct vaccination to help protect against RSV disease in children. There is a prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), that binds the RSV F glycoprotein, is recommended for use only in high-risk infants, and can prevent infant RSV disease.[13,14] A newer humanized monoclonal antibody targeting the prefusion conformation of RSV F glycoprotein, nirsevimab (Beyfortus, AstraZeneca and Sanofi), was recently approved to prevent RSV LRTD in neonates and infants born during or entering their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. However, antibodies that are currently licensed or in development for children <2 years of age may be impractical for older children because of the challenges around administration of an appropriate volume and the limited half-life compared to the period of risk in children up to 5 years of age. With the lack of antiviral therapies for treatment of RSV disease, the limited usefulness of monoclonal antibody prophylaxis, and the absence of a licensed vaccine to prevent RSV disease, there exists an unmet medical need for agents that can provide prophylaxis against RSV disease to children 2 to <5 years of age, and children 5 to <18 years of age who are at high risk of RSV-associated LRTI.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of RSVpreF may be found in the IB, which is the SRSD for this study.

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-Barré syndrome has been identified as a potential risk for RSVpreF. Other events of interest include atrial fibrillation, polyneuropathy, preterm birth, 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. 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-Barré syndrome and 1 case of Miller Fisher syndrome with a plausible temporal relationship with vaccination. Both cases had confounding factors or alternative etiologies. 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 the placebo. Most of the participants who had atrial fibrillation and received RSVpreF had a pre-existing 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).	• 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. • IRC to review all safety data. • All participants will be observed for at least 30 minutes after vaccination. • Specific references to risks and events of interest are 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
Study Intervention(s): RSVpreF		
	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 non-significant numerical imbalance in hypertensive disorders of pregnancy reported for participants who received RSVpreF compared to participants who received the placebo. The majority of preterm and hypertensive disorders occurred more than 30 days following vaccination.	
Theoretical risk for RSV enhancement.	RSVpreF is being evaluated in ongoing clinical studies. Pfizer's immunization approach circumvents the risk of vaccine-mediated disease enhancement that was observed in the 1960s following direct immunization of RSV-naive infants with an FI-RSV. 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. During preclinical studies, in a standard cotton rat infectious RSV challenge model, the FI-RSV showed pathological signs of causing disease enhancement, and the current Pfizer vaccine candidate, RSVpreF, did not. Unlike the FI-RSV, RSVpreF is an F glycoprotein subunit stabilized in the prefusion conformation. RSVpreF elicits strong neutralizing antibodies (and a high neutralizing to nonneutralizing ratio) as established in the adult studies and has	• Assessments of AEs and SAEs will be collected and reviewed throughout the study. • The study will be limited to seropositive children only and will assess the cellular response (Th1/Th2 balance) to RSVpreF. Th1- and Th2-specific cytokines will be used as a surrogate to characterize the cellular immune response and predisposition to enhanced disease. • Assessment of individual cases for disease enhancement is challenging based on current understanding of the mechanism of pathogenesis, thus evaluations of any adverse or unexpected imbalances in severe RSV cases may provide insight into a potential signal for this theoretical risk.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RSVpreF		
	already shown efficacy in preventing LRTI in older adults and severe LRTI in infants born to vaccinated mothers (refer to Section 2.2.1). Available evidence indicates that RSVpreF is efficacious and is unlikely to confer any risk of enhanced disease.	
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 a potentially efficacious RSV vaccine.
- 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

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability of RSVpreF at each dose level in children 5 to <18 years of age and children 2 to <5 years of age.	Prompted local reactions (pain at the injection site, redness, and swelling). Prompted systemic events (fever, vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain). AEs. SAEs. NDCMCs.	In participants receiving 1 dose of study intervention at each dose level, for each age stratum: • The percentage of participants reporting local reactions within 7 days after vaccination. • The percentage of participants reporting systemic events within 7 days after vaccination. • The percentage of participants reporting AEs from vaccination through 1 month after vaccination. • The percentage of participants reporting SAEs throughout the study. • The percentage of participants reporting NDCMCs throughout the study.

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
To describe the immune response elicited by RSVpreF at each dose level in children 5 to <18 years of age and children 2 to <5 years of age.	RSV A and RSV B NTs.	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • GMTs of NT for RSV A and RSV B 1 month after vaccination. • GMTs of NT for RSV A and RSV B before vaccination. • GMFRs of NT for RSV A and RSV B from before vaccination to 1 month after vaccination.
To describe the cell-mediated immune response in children 5 to <18 years of age and children 2 to <5 years of age.	RSV F antigen–specific CD4+ T cells secreting IFNγ. RSV F antigen–specific CD4+ T cells secreting IL-4.	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • Median frequencies of RSV F antigen–specific CD4+ T cells expressing IFNγ before vaccination and 1 month after vaccination. • Median frequencies of RSV F antigen–specific CD4+ T cells expressing IL-4 before vaccination and 1 month after vaccination.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, age-descending, dose-finding study of the safety, tolerability, and immunogenicity of RSVpreF in RSV-seropositive children 2 to <18 years of age. Participants will be divided into 2 age strata: 5 to <18 years and 2 to <5 years. All participants will receive 1 dose of RSVpreF.

A single dose of RSVpreF 120 µg will be administered to the older age stratum first. Upon confirmation of an acceptable safety assessment by the IRC, dose administration will proceed in the 2- to <5-year age stratum with 60 µg. Pending IRC approval, the younger age stratum will receive 120 µg of vaccine. The IRC may also request that a dose of RSVpreF 60 µg be given in the older age stratum.

Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose.

Stopping rules will apply as detailed in Section 8.3.5.

All participants within the 2- to <5-year age stratum will require a blood sample to be taken at the screening visit to assess serostatus, and only those who are seropositive can be enrolled and administered RSVpreF on Day 1. All participants 5 years of age and older will be considered RSV seropositive and will not require a screening test.

All participants will have blood drawn prior to vaccination on Day 1 and 1 month after vaccination to assess immune response elicited after vaccination with RSVpreF. An additional whole blood sample will be obtained prior to vaccination on Day 1 and 1 month after vaccination for PBMC isolation. An analysis of prespecified cytokines will be conducted to describe postvaccination cell-mediated immune responses 1 month after vaccination.

4.1.1. Number of Participants

This is an open-label dose-finding study. A single dose of RSVpreF 120 µg will be given to approximately 40 participants in the 5- to <18-year age stratum first, equally divided between healthy children and those with high-risk chronic medical conditions. Upon IRC approval, a dose of 60 µg will be given to 20 participants in the 2- to <5-year age stratum. If, per the IRC, 60 µg is safe and tolerable, another 20 participants in the 2- to <5-year age stratum will receive the 120-µg dose. The IRC may also request that a single dose of RSVpreF 60 µg be given to approximately 40 participants in the 5- to <18-year age stratum. Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose. Approximately 60 to 120 participants are expected to be enrolled in the Phase 1 cohort. See Table 1.

Table 1. Participants

Age Stratum (Years)	Number of Participants
2 to <5	~20/~20[a]
5 to <18	~40/~40[a,b]
Total	~60-120

a. Up to 2 dose levels of RSVpreF (120 µg and 60 µg) will be tested in participants.
b. Approximately 40 participants 5 to <18 years old will be enrolled in this study, with ~20 healthy participants and ~20 participants with high-risk chronic medical conditions receiving each dose level.

4.1.2. Intervention Groups and Duration

Dose finding will begin with 120 µg of RSVpreF in participants 5 to <18 years of age. The IRC will review safety data (e-diary and AEs) acquired up to 7 days after dose administration once a minimum of 10 and up to approximately 40 participants have been vaccinated. Upon confirmation of an acceptable safety assessment by the IRC, dose administration may commence with 60 µg in participants 2 to <5 years of age. The same process with an IRC review of safety data (e-diary and AEs) acquired up to 7 days after dose administration at the low-dose level from participants 2 to <5 years of age will be followed before administering the 120-µg dose to this younger stratum.

In the 2- to <5-year age stratum, if 60 µg is considered unacceptable based on the safety assessment, administration of the 120-µg dose level will not commence. In this case, an optional lower dose level may commence. Upon IRC review, RSVpreF 60 µg may also be given to participants in the 5- to <18-year age stratum.

Duration: The study duration for each participant will be approximately 6 months.

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics to ensure that the study population is representative of the population that will use RSVpreF in clinical practice.

4.3. Justification for Dose

The dose and formulation plan for this study is to start with 120 µg RSVpreF without any adjuvants in participants 5 to <18 years of age, before initiating the 60-µg dose level.

The FIH study in adults 18 through 85 years of age evaluated the safety, tolerability, and immunogenicity of 3 escalating RSVpreF dose levels of 60 µg, 120 µg, and 240 µg, with or without $Al(OH)_3$, when administered alone or concomitantly with SIIV (Study C3671001).

A study in older adults 65 through 85 years of age evaluated the safety, tolerability, and immunogenicity of 60-µg, 120-µg, and 240-µg RSVpreF doses formulated with $Al(OH)_3$ or a CpG/$Al(OH)_3$ adjuvant, or 240 µg RSVpreF with RSV antigens alone, when administered concomitantly with SIIV (Study C3671002).

A Phase 3 study in adults 65 years of age and older evaluated the safety, tolerability, and immunogenicity of 120 µg RSVpreF when administered concomitantly with SIIV (Study C3671006).

A study in healthy adults 18 through 50 years of age evaluated the safety, immunogenicity, and efficacy of 120 µg RSVpreF in a virus challenge model (NCT04785612).

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 the study only if all of the following criteria apply:

Age and Sex:

1. Participants 2 to <18 years of age at enrollment (signing of the ICD or providing assent to participate) at Visit 1.

Disease Characteristics:

2. Participants 2 to <18 years of age should either be healthy or be considered by the investigator to be at high risk of RSV disease based on the presence of 1 of the following chronic medical conditions[9,10,25]:

    - Cystic fibrosis
    - Medically treated asthma
    - Other chronic respiratory diseases and malformations of the lung
    - Down syndrome
    - Neuromuscular disease
    - Cerebral palsy

- Hemodynamically significant or symptomatic congenital heart disease

Details of the chronic medical conditions listed above are further defined in the investigator site file.

Other Inclusion Criteria:

3. All participants 2 to <5 years of age must be seropositive for RSV as confirmed by serology.

4. Participants' parent(s)/legal guardian(s) and participants, as age appropriate, who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, and other study procedures. Participants' parent(s)/legal guardian(s) should be available for telephone contact with site staff for the duration of the study.

5. The participant's parent(s)/legal guardian is capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).

5.2. Exclusion Criteria

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

Medical Conditions:

1. Immunocompromised individuals associated with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

2. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus. Note: Stable type 1 diabetes and hypothyroidism are permitted.

3. Other 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.

4. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

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

6. Individuals with a history of epilepsy or other seizure disorders, or a history of seizures and/or other neurological complications following vaccination.

Prior/Concomitant Therapy:

7. Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation. Children who may have been exposed to investigational RSV vaccines through maternal immunization will be permitted.

8. Receipt of investigational or approved monoclonal antibodies against RSV within 6 months before study intervention administration, or planned receipt throughout the study.

9. Receipt of blood/plasma products or immunoglobulins within 28 days before study intervention administration, or planned receipt throughout the study.

10. Receipt of chronic systemic treatment with known immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before study intervention administration, or planned receipt throughout the study.

    Note: Systemic corticosteroids are defined as those administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease). Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving study intervention within 28 days prior to study entry and/or for the duration of study participation.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

12. 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.

5.3. Lifestyle Considerations

There are no lifestyle restrictions required for the participants in this study.

All pregnancies discovered in female participants during the study participation, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded in the CRF in addition to completing the EDP (Section 8.4.5.1) and EDB (Section 8.4.5.2) reporting processes.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. 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, and any SAEs.

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

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

The following conditions may allow a participant to be vaccinated once the conditions have resolved and the participant is otherwise eligible:

- Current febrile illness (temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration.
- Receipt of any live vaccine within 28 days before study intervention administration. Receipt of any nonlive vaccine (including COVID-19 vaccines authorized for temporary or emergency use) within 14 days before study intervention administration.
- Anticipated receipt of any nonstudy vaccine within 14 days after study intervention administration at Visit 1 (before Day 15).
- Receipt of short-term (<14 days) systemic corticosteroids (equivalent of ≥20 mg/day of prednisone). 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, eyes, or ears) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to RSVpreF.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	PF-06928316 (RSVpreF)
Arm Name (group of participants receiving a specific vaccine or no vaccine)	Active vaccine group
Unit Dose Strength(s)	120 µg and/or 60 µg
Type	Vaccine
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 RSVpreF formulation will contain 120 µg of the RSV prefusion F antigen. RSVpreF 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. RSVpreF will be reconstituted by a diluent consisting of sterile water in a PFS. The lyophilized RSVpreF formulation contains excipients that, after reconstitution, will yield a solution as detailed in the IB. The fill volume of the RSVpreF vial and diluent PFS are designed such that the 120-µg vaccine dose is delivered by injecting the entire contents of the syringe. The 60-µg vaccine dose is delivered by injecting 0.25 mL of a graduated syringe content.
Route of Administration	Intramuscular
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	The vaccine will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

Study Arms(s)	
Arm Title	Active vaccine
Arm Type	Experimental

6.1.1. Administration

Participants will receive 1 dose of 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 (for 120 µg RSVpreF) or 0.25 mL of a graduated syringe content (for 60 µg RSVpreF) into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Study intervention administration will be performed by appropriately designated study staff at the investigator site.

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

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

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 (RSVpreF or placebo). 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.

All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 10.6) and appropriately managed by the sponsor.

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 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.

Study intervention will be prepared by qualified site personnel according to the IPM or package insert, and the study intervention will be administered in an open-label manner.

6.3. Assignment to Study Intervention

The study intervention to be dispensed to the participant will be assigned using an IRT system. The site will utilize the IRT system to assign the DU or container number(s) prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

Study intervention will be dispensed at the study visit(s) summarized in the SoA.

6.4. Blinding

6.4.1. Blinding of Participants

This is an open-label study. Participants and their caregivers will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

The study is open-label, and all site personnel, including the investigator, investigator staff, and study staff receiving, storing, dispensing, preparing, and administering the study interventions, will be unblinded.

Please refer to the IPM for further details.

6.4.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants throughout the study.

6.4.4. Breaking the Blind

Not applicable.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time, as well as the anatomical location of each dose administered in the clinic, will be recorded in the source documents, and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dose administration by a member of the study site staff other than the person administering the study intervention.

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.

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 at least until the next scheduled follow-up.
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**.

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

6.9. Prior and Concomitant Therapy

The following concomitant medications, vaccinations, and treatments will be recorded in the CRF:

- Any vaccinations received from 28 days prior to study enrollment until the last study visit.
- Prohibited medications and treatments listed in Section 6.9.1 if taken, will be recorded, including start and stop dates, name of the medication, dose, unit, route, and frequency.

6.9.1. Prohibited Concomitant Vaccinations and Treatments

- Receipt of any nonstudy RSV vaccine at any time prior to or during study participation.
- Receipt of investigational or approved monoclonal antibodies against RSV within 6 months prior to or during study participation.
- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study. Note: COVID-19 vaccines authorized for temporary, or emergency use will not be prohibited during the course of this study if administered more than 14 days prior to study intervention administration or at least 14 days (from Day 15 onwards) after study intervention administration.

- Receipt of blood/plasma products or immunoglobulin, from 28 days before study intervention administration and thereafter during the course of the study.

- Nonstudy vaccines may not be given concomitantly with the study intervention or within 14 days after study intervention administration (Day 1 through Day 14), except if medically necessary (eg, during an outbreak or pandemic situation).

- Receipt of chronic systemic treatment with known immunosuppressant medications other than systemic corticosteroids meeting the criteria noted below, within 60 days of administration of study intervention, through conclusion of the study.

- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through Day 28 after administration of study intervention (Day 1).

- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.9.2. Permitted Concomitant Vaccinations and Treatments

- Licensed vaccines may be given during the study starting 14 days after study intervention administration (Day 15).

- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

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

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

If a participant withdraws from the study, the participant's parent(s)/legal guardian may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

A participant may discontinue from the study procedure but continue to participate in protocol-specified AE-monitoring activities as outlined in Section 1.3, as long as the participant or participant's parent(s)/legal guardian does not withdraw consent.

If the participant's parent(s)/legal guardian or a child who has provided assent during any phase of the study withdraws from the study and also withdraws consent/assent (Section 7.2.1) for disclosure of further 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.

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

7.2.1. Withdrawal of Consent

Participants who request (or whose parent[s]/legal guardian requests) to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant or participant's parent(s)/legal guardian specifically withdraws consent for any further contact with them or persons previously authorized by the participant or participant's parent(s)/legal guardian to provide this information. Participants or participants' parent(s)/legal guardians 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 further receipt of study intervention or also from study procedures and/or postvaccination study 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 the participant or participant's parent(s)/legal guardian is unable to be contacted by the study site.

The following actions must be taken if a participant and participant's parent(s)/legal guardian fail to attend a required study visit:

- The site must attempt to contact the participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible. Counsel the participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule, and ascertain whether the participant's parent(s)/legal guardian wishes for the participant to and/or whether the participant 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's parent(s)/legal guardian (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's parent(s)/legal guardian continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative 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 date of birth 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.

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that 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.

The total blood sampling volume for individual participants in this study is expected to be no more than 40 mL.

8.1.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participations at scheduled visits per the SoA or unscheduled 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. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Procedures as indicated for unscheduled visits for fever or a Grade 3 or suspected Grade 4 reactions (Section 8.11).

Study participants or participants' parent(s)/legal guardians must be reminded to promptly notify site staff about any change in the participant's health status.

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Efficacy Assessments

There are no efficacy assessments in this study.

8.2.2. Immunogenicity Assessments

RSV serostatus will be determined for participants 2 to <5 years of age prior to vaccination at Visit 1.

Blood samples (approximately 5 mL per sample for children <10 years of age and 10 mL for children 10 to <18 years of age) will be collected from participants for immunogenicity testing at both Visit 1 and Visit 3 (refer to Section 1.3, SoA). RSV A– and RSV B–neutralizing antibody titers will be measured for each blood sample at each time point and reported as the NTs.

Additionally, all participants will provide blood samples for PBMCs (approximately 1 mL per year of age but no more than 10 mL), to be collected at both Visit 1 and Visit 3. PBMC samples will be used to characterize the cell-mediated immune response through measuring RSV F antigen–specific CD4+ T cells secreting IFNγ and F antigen–specific CD4+ T cells secreting IL-4. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

8.2.3. Biological Samples

Blood 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 testing of the participant's DNA will be performed using blood samples including those for PBMC isolation.

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

A clinical assessment, including medical history, will be performed on all participants at their first visit to establish a baseline. Significant medical history and observations from any physical examination will be documented in the CRF.

AEs and SAEs will be collected, recorded, and reported as defined in Section 8.4.

The participant will have his or her body temperature measured prior to each vaccination and will be observed for at least 30 minutes after vaccination. Any acute reactions within the first 30 minutes after administration of the study intervention will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever) that occur in the 7 days after administration of the study intervention. The e-diary device will prompt the participant or the participant's parent(s)/legal guardian to report these self-collected occurrences of local reactions and systemic events. These participant-reported local reactions and systemic events (including fever) are graded as described in Section 8.3.4.

8.3.1. Physical Examinations

A physical examination will be performed at Visit 1. A brief physical examination will include, at a minimum, measurement of height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey as applicable.

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

Physical examination findings collected during the study will be considered source data 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 (Appendix 2) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2. Vital Signs

The participant's prevaccination temperature will be measured as per usual clinical practice.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.3. Clinical Safety Laboratory Assessments

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

8.3.4. Reactogenicity Electronic Diary

The participant or participant's parent(s)/legal guardian will be required to complete a reactogenicity e-diary after each vaccination. These participants or participants' parent(s)/legal guardians will be asked to monitor and record local reactions, systemic events, and temperature for 7 days from the day of administration of the study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing an accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be continually available for review by investigators, Pfizer clinicians, and other selected study team members via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant or participant's parent(s)/legal guardian for any reactions ongoing on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

Please note that all provisioned e-diary devices must be collected at the end of Visit 3 (1-month follow-up visit) per the SoA.

8.3.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials,[26] with adaptations for applicability to healthy younger children.

8.3.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants or participants' parents/legal guardians will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary daily for 7 days (Days 1 through 7) after each vaccination. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant or participant's parent(s)/legal guardian will be requested to report that information. The investigator will enter this additional information in the CRF.

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in caliper units (measuring device units; range: 1 to 14 caliper units for participants ≥2 to <12 years of age and 1 to 21 caliper units for participants ≥12 to 18 years of age) for the first 7 days following vaccination (Days 1 through 7), and then categorized as absent, mild, moderate, or severe using the scale shown in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participants or participants' parent(s)/legal guardians as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 local reaction is reported in the reactogenicity e-diary (redness or swelling >14 caliper units for participants <12 years of age or >20 caliper units for participants ≥12 years of age; Grade 3 pain at the injection site), a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations (if applicable) will be discontinued in that participant.

Table 2. Local Reaction Grading Scale

	Participant Age	Mild (Grade 1)	Moderate (Grade 2)	Severe[a] (Grade 3)	Potentially Life-Threatening[b] (Grade 4)
Pain at the injection site	≥2 Years	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site
Redness	≥2 Years to <12 years	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis or exfoliative dermatitis
	≥12 Years	5 to 10 caliper units (or measuring device units) = >2.0 to 5.0 cm	11 to 20 caliper units (or measuring device units) = >5.0 to 10.0 cm	>20 caliper units (or measuring device units) = >10 cm	Necrosis or exfoliative dermatitis
Swelling	≥2 Years to <12 years	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
	≥12 Years	5 to 10 caliper units (measuring device units) = >2.0 cm to 5.0 cm	11 to 20 caliper units (measuring device units) = >5.0 cm to 10.0 cm	>20 caliper units (or measuring device units) = >10 cm	Necrosis

a. Parent(s)/legal guardians of participants <12 years of age experiencing local reactions >14 caliper units (>7 cm), participants or parent(s)/legal guardians of participants ≥12 years of age experiencing local reactions >20 caliper units (>10 cm), and parent(s)/legal guardians of participants experiencing Grade 3 pain at the injection site are to be contacted by the study site. An unscheduled visit may be required.
b. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

8.3.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardians will be asked to assess vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant or participant's parent(s)/legal guardian as absent, mild, moderate, or severe according to the grading scale in Table 3.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations (if applicable) will be discontinued in that participant.

Table 3. Systemic Event Grading Scale for Participants ≥2 Years of Age

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for severe vomiting
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
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue/tiredness
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 participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

8.3.4.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature ≥38.0°C (>100.4°F).

The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 4 during analysis.

If a fever of ≥39.0°C (≥102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations (if applicable) will be discontinued in that participant.

Table 4. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

8.3.5. Stopping Rules

The following stopping rules apply by age group and are in place for all participants, based on review of AE data and e-diary reactogenicity data, through 30 days after the administration of study intervention in each age group. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during the study, so they will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

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

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for all dose levels in the impacted age group.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of RSVpreF. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The RSVpreF dose levels within an age group will contribute to stopping rules collectively; vaccine candidate dose levels will contribute to stopping rules together.

Stopping Rule Criteria:

1. If any participant vaccinated with RSVpreF at any dose level develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any participant vaccinated with RSVpreF at any dose level develops a Grade 4 local reaction or systemic event after vaccination (Section 8.3.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any participant vaccinated with RSVpreF at any dose level develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination (see Section 8.3.4.4) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with RSVpreF at any dose level within the same age group report the same or similar severe (Grade 3) AE after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause. Note that the local reactions, systemic events, and fever specified in Section 8.3.4 reported within 7 days of (Day 1 through Day 7) administration of the study intervention, irrespective of whether they are recorded in the e-diary or as AEs, are excluded from this stopping rule.

5. If there is an ICU admission or participant death that is assessed by the investigator to be attributed to RSV infection, all available clinical and preclinical data should be reviewed to evaluate for RSV vaccine–elicited ERD.

8.3.6. Randomization and Vaccination After a Stopping Rule Is Met

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

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.6. 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 healthcare providers (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 the study (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant's parent(s)/legal guardian/legally authorized representative 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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant's parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures must be reported in the CRF.

SAEs, AESIs, and NDCMCs will be collected from the time the participant's parent(s)/legal guardian provides informed consent through the duration of the study.

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 participant 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 Vaccine SAE Reporting Form.

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 completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.4.1.1. 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 on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 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 participant.

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 Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant or participant's parent(s)/legal guardian 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 Appendix 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 healthcare providers, 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 female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- 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 healthcare provider reports that she is pregnant after having been exposed to the study intervention by inadvertent product administration via needlestick or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inadvertent product administration via needlestick 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 a participant/participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until the participant's last visit of the study.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. 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 Reporting Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. 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), 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). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by injection or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. 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 Vaccine SAE Reporting Form is maintained in the investigator site file.

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 using the Vaccine SAE Reporting Form, 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 Vaccine SAE Reporting Form must be maintained in the investigator site file.

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

- Diagnosis of Guillain-Barré syndrome
- Diagnosis of acute polyneuropathy without an underlying etiology
- Diagnosis of atrial fibrillation
- Preterm delivery (delivery at <37 0/7 weeks' gestation)
- Diagnosis of a hypertensive disorder of pregnancy

Details of the AESIs listed above are further defined in the investigator site file.

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 Sections 8.4.1 through Section 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 PSSA or using the Vaccine SAE Reporting Form. The active collection period for AESIs is from the signing of the ICD until the end of the study for all participants.

8.4.8.1. Lack of Efficacy

This section is not applicable for this study, as efficacy is yet to be demonstrated in the study population.

8.4.9. 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 Appendix 6.

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 Section 8.4.4 and Appendix 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.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

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

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by a contact method as detailed in the IPM within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. 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.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.4.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting Form as outlined in Section 8.4.1.1 and Section 8.4.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

8.4.10. 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 Vaccination Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the vaccination error	Only if associated with an SAE

Vaccination errors include:

1. Vaccination errors involving participant exposure to the study intervention;
2. Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
3. The administration of expired study intervention;
4. The administration of an incorrect study intervention;
5. The administration of an incorrect dosage;
6. The administration by an incorrect route;
7. The administration of 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.

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

Whether or not the vaccination error is accompanied by an AE, as determined by the investigator, the vaccination error is recorded on the vaccination error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, 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 on a Vaccine SAE Reporting Form **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 8.2.2.

8.9. Health Economics

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

8.10. Study Procedures

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

Voluntary, written, study-specific informed consent (from the participant's parent[s]/legal guardian), and assent (from the participant, where appropriate), will be obtained before enrollment and before any study-related procedures are performed. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent (and assent if appropriate) was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed **prior to administration of the investigational vaccine** are conducted prior to study vaccination. If screening and vaccination are not on the same day, all procedures listed as "on the day of and prior to vaccination" must be conducted prior to vaccination and on the day of the vaccination.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain the participant's medical history of clinical significance.
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, measurement of height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
    - For participants 2 to <5 years of age: This procedure must be repeated on the day of and prior to vaccination if serostatus results will not be available on the same day as vaccination.
- On the day of and prior to vaccination, measure the participant's temperature as per usual clinical practice.
    - For participants 2 to <5 years of age: This procedure must be repeated on the day of and prior to vaccination if serostatus results will not be available on the same day as vaccination.

- **All eligible participants will proceed to complete the vaccination visit.**

- Record nonstudy vaccinations as described in Section 6.9.
- Obtain details of prohibited medication used as described in Section 6.9.1.
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL for children <10 years of age and approximately 10 mL for children 10 to <18 years of age) for immunogenicity.
- On the day of and prior to vaccination, collect a blood sample for PBMC isolation.
- On the day of and prior to vaccination, children 2 to <5 years of age will have RSV serostatus tested.

  Note: Participants 2 to <5 years of age who are seropositive can be enrolled and administered RSVpreF on Day 1. All participants 5 years of age and older will be considered RSV seropositive and will not require a screening test.

- On the day of and prior to vaccination, obtain the participant's randomization number and study intervention allocation using the IRT system. Refer to the IRT manual for further instructions on this process.
- Qualified site staff member(s) will administer a single dose of 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 participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Explain the e-diary technologies available for this study (see Section 8.3.4) and assist the participant's parent(s)/legal guardian in downloading the study application onto his or her own device or issue a provisioned device if required.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Provide instructions on reactogenicity e-diary completion and ask the participant's parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (>102.1°F).

  - Redness or swelling at the injection site >14 caliper units (or >7 cm) for children <12 years old and/or >20 caliper units (or >10 cm) for children ≥12 years old.

  - Grade 3 pain at the injection site.

  - Any severe systemic event.

  - If the participant doesn't call, the site should contact the participant to determine if an unscheduled reactogenicity visit is required.

- Record AEs, SAEs, AESIs, and NDCMCs as described in Section 8.4.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Schedule an appointment for the participant's next study visit.

- 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 appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.2. Visit 2 – 1-Week Follow-Up Visit (Telehealth; 6 to 8 Days After Vaccination on Day 1)

- Contact the participant's parent(s)/legal guardian by telephone.

- Obtain details of any nonstudy vaccinations and prohibited concomitant medications and treatments as described in Section 6.9.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record AEs, SAEs, AESIs, and NDCMCs as described in Section 8.4.
- Schedule an appointment for the participant's next study visit.
- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.3. Visit 3 – 1-Month Follow-Up Visit (Clinic; 28 to 35 Days After Visit 1)

- Obtain details of any nonstudy vaccinations and prohibited concomitant medications and treatments as described in Section 6.9.
- Collect a blood sample (approximately 5 mL for children <10 years of age and approximately 10 mL for children 10 to <18 years of age) for immunogenicity.
- Collect a blood sample for PBMC isolation.
- Review ongoing reactogenicity e-diary symptoms reported as present on the last day of the e-diary and obtain stop dates. Record stop dates in the CRF if required.
- Record AEs, SAEs, AESIs, and NDCMCs as described in Section 8.4.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device (if this has not been done already).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.4. Visit 4 – 6-Month Follow-Up Visit (Telehealth; 175 to 189 Days After Visit 1)

- Contact the participant's parent(s)/legal guardian by telephone.
- Obtain details of any nonstudy vaccinations as detailed in Section 6.9.

- Record details of any of the prohibited medications specified in Section 6.9.1. Review ongoing reactogenicity e-diary symptoms reported as present on the last day of the e-diary and obtain stop dates. Record stop dates in the CRF if required.
- Record SAEs, AESIs, and NDCMCs as described in Section 8.4.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11. Unscheduled Visit for Fever or a Grade 3 or Suspected Grade 4 Reaction

If a participant or participant's parent(s)/legal guardian reports redness or swelling >14 caliper units (or >7 cm) for participants <12 years of age and >20 caliper units (or >10 cm) for participants ≥12 years of age or a Grade 3 local reaction (Table 2), any Grade 3 systemic event (Table 3), or fever >39.0°C (102.1°F) (Table 4) in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction (Table 2), systemic event (Table 3), or fever >40.0°C (>104.0°F) (Table 4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4. A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or participant's parent(s)/legal guardian recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.
- This telephone contact (or site visit) will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Table 2.
- Assess systemic events (if present) in accordance with the grades provided in Table 3.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.12. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or participant's parent(s)/legal guardian is maintained so that safety events or endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained, and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or participant's parent(s)/legal guardian and the study site staff will be established. The participant or participant's parent(s)/legal guardian may be able to utilize his or her own device to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (e-diary). See Section 8.3.4.

If a participant or participant's parent(s)/legal guardian is not actively completing the reactogenicity e-diary, the investigator or designee is required to contact the participant or participant's parent(s)/legal guardian to ascertain the reason and also to obtain details of any missed events.

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

There is no statistical hypothesis testing in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	All participants who have a signed ICD.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive the study intervention.

Defined Analysis Set	Description
Evaluable immunogenicity population	This population will be defined as all participants who meet the following criteria: • Are eligible for the study; • Receive the intervention; • Have the 1-month postvaccination blood collection within an appropriate window; • Have at least 1 valid and determinate assay result 1 month after vaccination; • Have no major protocol violations from vaccination through the 1-month postvaccination blood draw.
mITT immunogenicity population	All participants who are randomized and have at least 1 valid and determinate assay result at any time point after receiving study intervention.

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

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 partially complete e-diary data (ie, 1-6 days of reactogenicity data are available), it is expected that these missing e-diary days would be queried by the investigator, and any missed reported reactogenicity would be entered in the AE CRF; therefore, the primary analysis will use the reactogenicity recorded in the AE CRF to impute the partially missed e-diary data to estimate the reactogenicity rates during the 7-day period.

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.

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 exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[27]

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 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. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the line first going down and then to the right to the next assay value.

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

Table 5. Primary Endpoint Analyses

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each RSVpreF dose level within each age stratum. Local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, fatigue/tiredness, headache, vomiting, diarrhea, 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 of the AEs within 1 month and SAEs/NDCMCs throughout the study will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CIs for each RSVpreF dose level within each age stratum (Section 9.3.1.1). • Descriptive summaries may also be provided for the combined age group (2 to <18 years) within the same RSVpreF dose level.

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

Table 6. Secondary Endpoint Analyses

Endpoint	Statistical Analysis Methods
Immunogenicity	• GMTs before vaccination and 1 month after vaccination will be descriptively summarized with 2-sided 95% CIs for each RSVpreF dose level within each age stratum for both RSV A and RSV B subgroup NTs (Section 9.3.1.2.1). • GMFRs from before vaccination to 1 month after vaccination will be descriptively summarized with 2-sided 95% CIs for each RSVpreF dose level within each age stratum for both RSV A and RSV B subgroup NTs (Section 9.3.1.2.2). • GMTs, GMFRs, and associated 95% CIs may also be descriptively summarized for the combined age group (2 to <18 years) for each RSVpreF dose level for both RSV A and RSV B subgroup NTs. • The frequency of CD4+ T cells expressing IFNγ and the frequency of CD4+ T cells expressing IL-4 before vaccination and 1 month after vaccination will be descriptively summarized.

9.4. Interim Analyses

No interim analysis is planned.

9.4.1. Analysis Timing

As Phase 1 is open-label, the sponsor may conduct reviews of the data during the study for the purpose of decision making.

One final analysis will be performed when all data are cleaned.

9.5. Sample Size Determination

Phase 1 enrollment is not based on a statistical criterion.

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/Assent Process

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited, they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardians must be informed that their participation is voluntary. The participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

The participant's parent(s)/legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardians in certain regions.

The source documentation must include a statement that written informed consent, and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

If participants are rescreened, the participants' parent(s)/legal guardians or the participants, where appropriate, are required to sign a new ICD/assent (as applicable).

10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

10.1.3.2. Remote Consent

Participants may be able to experience the informed consent process at their location rather than in person at the site. There are 2 types of remote consent, both of which involve the participant not being physically present with the study investigator or delegated site staff: (1) obtaining consent with the active participation of a PI or delegated site staff during the consenting process; and (2) obtaining consent without the active participation of a PI or delegated site staff, such as a via a healthcare website or portal.

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 IRC. The IRC is independent of the study team and includes only internal (IRC) members. The IRC charter describes the role of the IRC in more detail.

The responsibility of the IRC will include at a minimum:

- Review of safety data in the case of a stopping rule being met.
- Review of safety data accumulated for up to 7 days following vaccination of the 5- to <18-year age group to make a recommendation for commencing dose administration in the 2- to <5-year age group.
- Review of safety data accumulated for up to 7 days following vaccination of the 2- to <5-year age group to make a recommendation for dose escalation.
- Review of safety and immunogenicity data accumulated from 7 days following vaccination of both the 2- to <5-year and 5- to <18-year age groups to make a recommendation for dose selection for Phase 2/3.
- Review of safety and immunogenicity data accumulated for 1 month following vaccination.

The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the IRC 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, 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 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 on-site monitoring), are provided in the data management plan and monitoring plan 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, birthdate, 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), 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 ECs/IRBs, 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 participant 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 primary completion date 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) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) 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 laboratory 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 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.

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.

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

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the 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)* 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 AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, 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 using the Vaccine SAE Reporting Form.

- 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 Vaccine SAE Reporting Form/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.

- 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:

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE 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 Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally 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. • If the electronic system is unavailable, then the site will use the paper SAE DCT (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 off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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

10.3. Appendix 3: Contraceptive and Barrier Guidance

Not applicable.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors". In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × 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 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × 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 ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR 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 ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN or if the value reaches ≥3 × 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, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/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, 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 defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.5. Appendix 5: Kidney Safety Monitoring Guidelines

10.5.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.5.2. Age-Specific Kidney Function Calculation Recommendations

10.5.2.1. Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula

CrCl (mL/min)

Males: Cr/Cl = [(140 - age) × body weight (in kg)] / [Scr (in mg/dL) × 72]

Females: Cr/Cl = 0.85 × [(140 - age) × body weight (in kg)] / [Scr (in mg/dL) × 72]

10.5.2.2. Children (2 Years to <12 Years)—Modified Schwartz Equation

CrCl normalized to BSA (mL/min/1.73 m^2) = (K × Ht) / Scr

Ht in centimeters; Scr in mg/dL.

K (proportionality constant): Female child <12 years: K = 0.55.

Male child <12 years: K = 0.70.

10.5.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.6. Appendix 6: 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).

10.6.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 2 (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.

10.6.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 2 (Section 10.2.2).
SADE Definition
• A 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 Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.6.3. 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.

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

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • 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. • If the investigator 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 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. Requirements for recording and reporting an AE or SAE are provided in Appendix 2 (Section 10.2.3). • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.   • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of 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 and/or product information, for marketed products, 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. • 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
• 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 healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 2.

10.6.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 2 (Section 10.2.4).

10.6.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, a 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.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BSA	body surface area
CBER	Center for Biologics Evaluation and Research (United States)
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations (United States)
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
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
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document

Abbreviation	Term
EMEA	European Medicines Agency
ERD	enhanced respiratory disease
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIPAA	Health Insurance Portability and Accountability Act
Ht	height
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IFNγ	interferon γ
IL-4	interleukin-4
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
IRC	internal review committee
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous
K	proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
LRTD	lower respiratory track disease
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness

Abbreviation	Term
MA-LRTI	medically attended lower respiratory tract illness
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MQI	medically qualified individual
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NT	neutralizing titer
PACL	protocol administrative change letter
PBMC	human peripheral blood mononuclear cell
PFS	prefilled syringe
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RTI	respiratory tract illness
RTI-RSV	RSV-associated respiratory tract illness
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
Tdap	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
Th1	T-helper type 1
Th2	T-helper type 2

Abbreviation	Term
UK	United Kingdom
ULN	upper limit of normal
US	United States
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
USPI	United States prescribing information
VE	vaccine efficacy
WHO	World Health Organization

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