A PHASE 3 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN OLDER ADULTS IN KOREA

Study Intervention Number:	PF-06928316
Study Intervention Name:	Respiratory Syncytial Virus (RSV) Vaccine
US IND Number:	N/A
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT06593587
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3671053
Phase:	3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Safety and Immune-Response Study of RSVpreF in Older Adults in Korea

Document History

Document	Version Date
Amendment 1	17 March 2025
Original protocol	05 April 2024

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). These changes to the protocol were communicated to investigators and IRBs/ECs prior to the initiation of study enrollment.

Protocol Amendment Summary of Changes Table

Amendment 1 (17 March 2025)

Overall Rationale for the Amendment:

To synthesize the original protocol, dated 05 April 2024, and 2 protocol administrative change letters (PACL 1, dated 11 July 2024, and PACL 2, dated 01 August 2024) for the licensure application to the Korean regulatory authority (MFDS).

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Not applicable		
Nonsubstantial Modification(s)		
Added ClinicalTrials.gov ID	Administrative	Title Page Section 1.1 Synopsis
Changed exclusion criterion 1 from 120 days to 180 days	Updated per PACL 2 (01 Aug 2024) at MFDS request	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
Extended the arrow and background color indicating local reactions and systemic events for Visit 2	Updated per PACL 1 (11 Jul 2024) at MFDS request	Section 1.2 Schema

Description of Change	Brief Rationale	Section # and Name
Added the administered dose volume and storage conditions for study intervention	Updated per PACL 1 (11 Jul 2024) at MFDS request	Section 6.1 Study Intervention(s) Administered Section 6.1.1 Administration
Updated text to clarify that the site is to collect the date of birth rather than year of birth	Updated per PACL 1 (11 Jul 2024) at MFDS request	Section 1.3 Schedule of Activities Section 8.1 Administrative Procedures Section 8.10.1 Visit 1 (Day 1 – Vaccination)
Added weight and height at Visit 1, and included a routine physical examination (including respiratory rate) at Visit 1, Visit 3, and unscheduled reactogenicity visit(s)	Updated per PACL 1 (11 Jul 2024) and PACL 2 (01 Aug 2024) at MFDS request	Section 1.3 Schedule of Activities Section 8.3 Safety Assessments Section 8.3.1 Physical Examinations Section 8.10.1 Visit 1 (Day 1 – Vaccination) Section 8.10.3 Visit 3 (1-Month Follow-Up) Section 8.10.5 Unscheduled Reactogenicity Visit
Deleted the option for eConsent	Updated per PACL 1 (11 Jul 2024) at MFDS request	Section 10.1.3.1 Electronic Consent

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Older Adults in Korea

Brief Title: A Safety and Immune-Response Study of RSVpreF in Older Adults in Korea

Regulatory Agency Identification Number(s):

US IND Number:	N/A
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT06593587
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3671053
Phase:	3

Rationale:

Respiratory syncytial virus (RSV) is an important cause of respiratory illnesses associated with a high rate of morbidity and mortality in older adults, especially in those with chronic cardiac and pulmonary diseases. Recent epidemiology studies conducted in the Republic of Korea revealed that RSV infection in older adults remains a concern. In Korea, there is currently no licensed vaccine to prevent RSV illness, and treatment of RSV infection consists primarily of supportive care.

Pfizer has developed an RSV vaccine, RSV stabilized prefusion F subunit vaccine (RSVpreF), to protect against the global burden of RSV-associated lower respiratory tract illness (LRTI-RSV) in older adults and infants. The vaccine, RSVpreF, contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. Studies of RSVpreF in both the older adult (Study C3671013) and maternal (Study C3671008) populations met their respective efficacy primary endpoints, and the vaccine has been shown to be well tolerated in both populations. Based on these studies, RSVpreF has received marketing authorization for use by the United States (US) Food and Drug Administration (FDA) and the European Commission, as well as other regulatory agencies. However, there are limited data on the safety and immunogenicity of RSVpreF in the Korean population. Demonstration of safety and immunogenicity in this study may support licensure of the RSV vaccine for other populations with unmet medical need, such as immunocompromised and high-risk adults, and infants via maternal vaccination.

After RSV natural infection, immunity is considered to be short-lived. Currently, there is no licensed vaccine to prevent RSV disease in older adults, and there are no specific effective treatments for RSV in Korea. Therefore, there is an important unmet medical need to develop an effective vaccine to boost the immune response sufficiently to protect older adults against RSV disease in Korea.

Given the significant unmet medical need in Korea and the efficacy and safety of RSVpreF demonstrated in global studies, this study will be conducted to evaluate the safety, tolerability, and immunogenicity of RSVpreF in Korean older adults to support a licensure application in Korea.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety profile of RSVpreF when administered to Korean adults ≥60 years of age	• Local reactions (redness, swelling, and pain at the injection site) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) • Adverse events (AEs) • Serious adverse events (SAEs) • Newly diagnosed chronic medical conditions (NDCMCs)	In participants receiving the study intervention, the percentage of participants reporting: • Local reactions within 7 days after vaccination • Systemic events within 7 days after vaccination • AEs within 1 month after vaccination • SAEs throughout the study • NDCMCs throughout the study
Immunogenicity		
To describe the immune responses to respiratory syncytial virus subgroup A (RSV A) and respiratory syncytial virus subgroup B (RSV B) elicited by RSVpreF in Korean adults ≥60 years of age	• RSV A and RSV B serum neutralizing titers (NTs)	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • Geometric mean titer (GMT) of NTs for RSV A and RSV B at each blood sampling visit • Geometric mean fold rise (GMFR) of NTs for RSV A and RSV B from before vaccination to 1 month after vaccination
Secondary:	**Secondary:**	**Secondary:**
Immunogenicity		
To further describe the immune responses to RSV A and RSV B elicited by RSVpreF in Korean adults ≥60 years of age	• RSV A and RSV B serum NTs	Seroresponse[a] rate of NTs for RSV A and RSV B at 1 month after vaccination

a. Seroresponse is defined as a postvaccination NT ≥4 times the lower limit of quantitation (LLOQ) if the baseline titer is below the LLOQ; or a ≥4-fold rise from baseline if the baseline titer is ≥ LLOQ.

Overall Design:

This is a Phase 3, randomized, double-blinded, placebo-controlled, multicenter trial to describe the safety, tolerability, and immunogenicity of bivalent RSVpreF in adults 60 years of age and older in Korea.

Number of Participants:

Approximately 360 study-eligible participants will be randomized to receive RSVpreF 120 µg or placebo in a 2:1 ratio. Randomization will be stratified by 3 age groups (60 through 69, 70 through 79, and ≥80 years), with approximately 100 participants to be enrolled in the 70- through 79-year and ≥80-year age strata combined. Study arms, blood draws, and safety assessment timings are presented below.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to the study intervention.

Study Population:

Inclusion Criteria

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

Age and Sex:

1. Participants 60 years of age or older at Visit 1.

    - Male participants able to father children must agree to use a highly effective method of contraception from the time of informed consent through at least 28 days after study intervention administration (see Section 10.3.1).

    - Female participants must not be of childbearing potential (see Section 10.3.3).

Disease Characteristics:

2. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

    Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infections with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in this protocol.

3. Participants who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, frequent symptom assessment by mobile device application (e-diary), and other study procedures.

4. Participants who are ambulatory and live in the community, or in assisted-living or long-term care residential facilities that provide minimal assistance, such that the participant is primarily responsible for self-care and activities of daily living (ADL).

Other Inclusion Criteria:

5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and the protocol.

Exclusion Criteria

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

Medical Conditions:

1. A confirmed diagnosis of RSV infection ≤180 days before study intervention administration.

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

3. Prior history of any subtype of Guillain-Barré syndrome (GBS) of any etiology.

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) or any related vaccine.

5. Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.

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

7. Any medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Individuals who receive chronic systemic treatment with immunosuppressive therapy (other than systemic corticosteroids meeting the criteria noted below), including cytotoxic agents, immunosuppressive monoclonal antibodies, or radiotherapy, eg, for cancer or an autoimmune disease, from 60 days before study intervention administration or planned receipt throughout the study.

   Note:

   - Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days from 28 days before study intervention.

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

9. Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration.

10. Previous vaccination with any licensed or investigational RSV vaccine, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

11. Previous administration with an investigational product (drug or vaccine) within 6 months prior to study intervention administration. Participation in other studies involving an investigational product (drug or vaccine) at any time during participation in this study.

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 Intervention(s)		
Intervention Name	RSVpreF	Placebo
Type	Vaccine	Placebo
Use	Experimental	Placebo
Investigational Medicinal Product (IMP) or Noninvestigational Medicinal Product	IMP	IMP

Study Intervention(s)		
(NIMP)/Auxiliary Medicinal Product (AxMP)		
Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Lyophile match/sterile water for injection
Unit Dose Strength(s)	120 µg	Not applicable (N/A)
Dosage Level(s)	120 µg	N/A
Route of Administration	IM	IM
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	RSVpreF is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a prefilled syringe (PFS) of sterile water diluent for injection (supplied). Study intervention(s) will be labeled as per country requirements.	Placebo is supplied as a lyophilized white cake containing excipients but no active ingredients, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Study intervention(s) will be labeled as per country requirements.
Single Reference Safety Document (SRSD)	Investigator's brochure (IB)	IB
Arm Title	**RSVpreF** Participants will receive RSVpreF 120 µg at Visit 1.	**Placebo** Participants will receive placebo at Visit 1.
Study Duration	Study duration for each participant is approximately 2 months from signing of the informed consent to the final visit.	

Statistical Methods:

Since this study is descriptive in nature, the planned sample size is not based on any statistical hypothesis testing.

The safety primary objective for the study will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs (including adverse events of special interest [AESIs]), NDCMCs, and SAEs after vaccination.

GMTs of NT for RSV A and RSV B measured at each blood sampling visit, and GMFRs of NT for RSV A and B from before vaccination to 1 month after vaccination, will be descriptively summarized with associated 2-sided 95% confidence intervals (CIs).

Ethical Considerations:

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

RSVpreF is an F glycoprotein subunit stabilized in the prefusion conformation, eliciting strong neutralizing antibodies as established in the adult studies, and has already shown efficacy in preventing lower respiratory tract illness (LRTI) in older adults.

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

- 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.

- GBS. In Study C3671013, conducted in adults 60 years of age and older, there were 2 cases of GBS or its variants identified with a plausible temporal relationship with vaccination among >18,000 individuals who received RSVpreF. Both cases had confounding factors or an alternative etiology.

- Other events of special interest include atrial fibrillation and polyneuropathy.

The study procedure–related risks include:

- Venipuncture, which will be performed during the study.

Further details on RSVpreF risks and AESIs are available in this protocol.

1.2. Schema

Table 1. Study Design

~360 Healthy adults ≥60 years of age randomized 2:1	**Visit 1 (Day 1) Vaccination**	**Visit 2 1-Week Follow-Up Telephone Call** 7-13 Days After Vaccination	**Visit 3 1-Month Follow-Up Blood Draw** 28-35 Days After Vaccination	**Visit 4 2-Month Follow-Up Telephone Call** 56-70 Days After Vaccination
Study Groups				
Group 1 RSVpreF n = 240				
Group 2 Placebo n = 120				
Safety				
Local reactions and systemic events[a]	Days 1 to 7 after vaccination			
AEs	Informed consent to Month 1			
AESIs SAEs NDCMCs	Informed consent to Month 2			

 Immunogenicity blood draw

 Study intervention administration

 Telephone contact for safety data

a. Collected for 7 days, or longer for ongoing symptoms, after study intervention until symptom resolution.

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.

Table 2. Schedule of Activities

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Reactogenicity Visit	Notes
Visit Description	**Day 1 Vaccination**	**1-Week Follow-Up**	**1-Month Follow-Up**	**2-Month Follow-Up**	**Safety Assessment**	
Visit Window (Days)		**7 to 13 Days After Vaccination**	**28 to 35 Days After Vaccination**	**56 to 70 Days After Vaccination**	**N/A**	Day relative to study intervention administration (Day 1)
Type of Visit						 : Clinic visit,  : Phone visit
Obtain written informed consent	X					Written informed consent must be obtained prior to undergoing any study procedures.
Obtain the participant's study number using the IRT system	X					Participant must be present and consented prior to obtaining the study number.
Record demography	X					Birth date, sex, race, and ethnicity.
Record significant medical history	X					
Record current/former tobacco usage	X					

Table 2. Schedule of Activities

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Reactogenicity Visit	Notes
Visit Description	**Day 1 Vaccination**	**1-Week Follow-Up**	**1-Month Follow-Up**	**2-Month Follow-Up**	**Safety Assessment**	
Visit Window (Days)		**7 to 13 Days After Vaccination**	**28 to 35 Days After Vaccination**	**56 to 70 Days After Vaccination**	**N/A**	Day relative to study intervention administration (Day 1)
Type of Visit						 : Clinic visit,  : Phone visit
Perform a clinical assessment and a physical examination	X		X		X	Includes measurement of temperature, heart rate, respiratory rate, and seated blood pressure. See Section 8.3.1 and Section 8.10.5 for further details.
Review prior vaccination history	X					Review vaccination history in source documents to verify eligibility and prohibited prior vaccinations. Record 28 days of vaccination history in the CRF. See Section 6.9.
Record any new nonstudy vaccinations		X	X	X	X	See Section 6.9.3.
Collect details of prohibited medications and treatments	X	X	X	X	X	See Section 6.9.1.
Confirm eligibility	X					See Section 5.
Confirm use of appropriate contraceptives (if applicable)	X	X	X			See Section 10.3.1.
Obtain prevaccination temperature	X					Oral, tympanic, or temporal artery.
Confirm no temporary vaccination delay criteria have been met	X					See Section 5.5.

Table 2. Schedule of Activities

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Reactogenicity Visit	Notes
Visit Description	**Day 1 Vaccination**	**1-Week Follow-Up**	**1-Month Follow-Up**	**2-Month Follow-Up**	**Safety Assessment**	
Visit Window (Days)		**7 to 13 Days After Vaccination**	**28 to 35 Days After Vaccination**	**56 to 70 Days After Vaccination**	**N/A**	Day relative to study intervention administration (Day 1)
Type of Visit						 : Clinic visit,  : Phone visit
Obtain the randomization number and container/kit number using the IRT system	X					Do not randomize until the participant is physically present and their eligibility has been confirmed.
Collect a blood sample of approximately 20 mL for antibody assessment	X[a]		X			a. Visit 1 sample is collected prior to vaccination.
Prepare and administer the study intervention as an IM injection into the deltoid muscle of the nondominant arm (preferable)	X					Refer to the IPM for instructions.
Observe the participant for acute reactions for a minimum of 30 minutes after vaccination	X					Any reactions occurring in the 30-minute period after vaccination must be recorded on the CRF, **including the time of onset.** Treat reactions as clinically indicated.
Provide a digital thermometer and a measuring device	X					
Assist the participant with downloading the e-diary application, or issue provisioned device, if required	X					E-diary data (local reactions and systemic events) are collected for 7 days, or longer for ongoing symptoms, after study intervention.

Table 2. Schedule of Activities

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Reactogenicity Visit	Notes
Visit Description	**Day 1 Vaccination**	**1-Week Follow-Up**	**1-Month Follow-Up**	**2-Month Follow-Up**	**Safety Assessment**	
Visit Window (Days)		**7 to 13 Days After Vaccination**	**28 to 35 Days After Vaccination**	**56 to 70 Days After Vaccination**	**N/A**	Day relative to study intervention administration (Day 1)
Type of Visit						 : Clinic visit,  : Phone visit
Provide e-diary training on the daily reactogenicity questionnaire	X					
Review reactogenicity e-diary data	X	X				E-diary data are transmitted daily to a Web-based portal for review by the investigator or delegate (preferably on a daily basis) during the 7-day e-diary follow-up period. Assess and manage any noncompliance.
Ask the participant to contact site staff in the event of any severe local reactions or systemic events in the 7-day e-diary follow-up period	X					If the participant does not call, site staff must contact the participant to determine whether an unscheduled reactogenicity visit is required.
Remind the participant to bring their e-diary/smartphone to the next study visit	X	X				
Collect stop dates for any symptoms marked as ongoing on the last day of the e-diary collection period in the CRF		X	X	X		

Table 2. Schedule of Activities

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Reactogenicity Visit	Notes
Visit Description	**Day 1 Vaccination**	**1-Week Follow-Up**	**1-Month Follow-Up**	**2-Month Follow-Up**	**Safety Assessment**	
Visit Window (Days)		**7 to 13 Days After Vaccination**	**28 to 35 Days After Vaccination**	**56 to 70 Days After Vaccination**	**N/A**	Day relative to study intervention administration (Day 1)
Type of Visit						 : Clinic visit,  : Phone visit
Ensure all e-diary data have been transferred, collect provisioned e-diary, or assist participant with deleting the application, as appropriate			X			Do not deactivate the e-diary until all data are confirmed as having been transferred to the e-diary data management system.
Obtain details and record any AEs	X	X	X		X	See Section 8.4.2.
Obtain details and record any AESIs	X	X	X	X	X	See Section 8.4.8.
Obtain details and record any SAEs and NDCMCs	X	X	X	X	X	See Section 8.4.2.
Measure minimum and maximum diameter of redness (if present) or swelling (if present)					X	
If present, assess the severity of necrosis or exfoliative dermatitis at the injection site					X	
If present, assess the severity of any injection site pain					X	
If present, assess the severity of any systemic event (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain)					X	

Table 2. Schedule of Activities

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Reactogenicity Visit	Notes
Visit Description	**Day 1 Vaccination**	**1-Week Follow-Up**	**1-Month Follow-Up**	**2-Month Follow-Up**	**Safety Assessment**	
Visit Window (Days)		**7 to 13 Days After Vaccination**	**28 to 35 Days After Vaccination**	**56 to 70 Days After Vaccination**	**N/A**	Day relative to study intervention administration (Day 1)
Type of Visit						 : Clinic visit,  : Phone visit
If applicable, review any hospital or emergency room visits for management of postvaccination local reactions or systemic events					X	
Complete the source documents and CRFs	X	X	X	X	X	

2. INTRODUCTION

RSV is a major cause of respiratory infection in individuals of all ages, and can result in severe illness in infants, older adults, and those with health conditions that put them at increased risk of severe RSV and complications. The burden of RSV disease is also significant in children, in the immunocompromised, and in those with underlying comorbidities at high risk of severe RSV disease.

There are 2 antigenic variants of RSV, RSV A and RSV B, that cocirculate.[1] Like influenza, RSV infection follows a seasonal pattern, causing yearly wintertime epidemics in temperate climates, usually between late fall and early spring. In tropical climates, the outbreaks are generally associated with rainy seasons but are more unpredictable and frequently continuous.[2]

Older adults ≥60 years of age are at increased risk of RSV infection, which can trigger exacerbations of underlying comorbid conditions such as COPD and CHF. In the US, RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalizations for COPD exacerbations.[3]

RSV in Korea

Data on the epidemiology of RSV in Korean adults show that RSV is a common causative pathogen in ARI (including ILI) or pneumonia. In a nationwide passive surveillance study of viruses causing ARI from 36 sentinel hospitals, the RSV positivity rate was 2.78% among adult patients with respiratory viruses, of which 22.76% were over 65 years of age.[4] Another surveillance study in Korea from 2009 to 2014 with outpatient respiratory samples reported a similar RSV detection rate of 1.6% (3/183) among adults over 65 years of age.[5]

Rates of RSV-related hospitalization cases in clinical surveillance averaged 280.7/week from January 2016 to January 2020, which was comparable to the influenza-related hospitalization weekly rate.[6] RSV infection was found in 1.1% of adults hospitalized for ARI,[7] and in 2.3% of adults with suspected viral acute respiratory infections (mean age 70 years).[8] Among adult patients with severe pneumonia admitted to the ICU (mean/median age approximately 65 years), RSV was detected in 5.1% to 6.1% of those tested.[9,10,11] In one of these studies of pneumonia patients requiring ICU admission, RSV was significantly more common in those with CAP compared to patients with HCAP (10.9% vs 2.2%, p = 0.01). Generally, RSV A is more prevalent than RSV B in Korean adults.[9,12,13]

There are limited data on the clinical outcomes of RSV disease in older adults in Korea. However, 1 study in adults ≥65 years old hospitalized with RSV-associated pneumonia reported a 30-day in-hospital mortality rate of 12.0% (9/75), an admission rate to the ICU of 26.7% (20/75), and an average hospital stay of 20.4 days.[12] Another study in adults hospitalized with RSV infection (average age 70 years) or influenza (average age 62 years) has shown RSV infection to be associated with a significantly higher risk of death (20-day all-cause mortality rate 18.4% vs 6.7%; hazard ratio 2.32; 95% CI 1.17-4.58) when compared with influenza patients in the same hospital, and that RSV patients were more likely to be

residents of a long-term care facility or to have COPD, pneumonia, or respiratory bacterial superinfection.[8] Comorbidities are common in adults hospitalized for ARI with RSV infection (75%-80%), and coinfection with other pathogens (eg, coronavirus, influenza, rhinovirus, or bacteria) is also more common in adults than children (44.4% vs 3.0% for RSV A coinfection), which may lead to longer hospital stays and higher risk of life-threatening infections or death.[14,15] However, the burden of adult RSV disease could be underestimated since testing for RSV is less common in older adults than in children. RSV disease in adults is also difficult to diagnose based on clinical signs and symptoms alone, and, before the broader use of more sensitive detection methods, laboratory confirmation of RSV in adults was challenging because of low levels of virus shedding.[3]

RSV disease management in adults is limited to supportive measures such as hydration and oxygenation. Aerosolized ribavirin has limited evidence of effectiveness and is predominantly restricted to hospitalized, severely immunocompromised patients because of inconvenient administration, teratogenicity and anemia concerns, and high cost. Prevention of RSV disease via active immunization has the potential to make a significant impact in older adults, therefore making vaccine development a high priority.[16,17]

2.1. Study Rationale

Pfizer has developed an RSV vaccine, RSVpreF, to protect against the global burden of LRTI-RSV in older adults and infants. RSVpreF contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. Studies of RSVpreF in both the older adult and maternal populations met their respective efficacy primary endpoints, and the vaccine has been shown to be well tolerated in both populations.

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

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

The FDA approved RSVpreF (Abrysvo®) for marketing for individuals 60 years of age and older and pregnant individuals on 31 May 2023 and 21 August 2023, respectively. A marketing authorization for Abrysvo to help protect both infants through maternal immunization and older adults was granted by the European Commission on 23 August 2023, by the MHRA on 21 November 2023, and by Health Canada on 21 December 2023. RSVpreF was approved for use in Japan for pregnant individuals on 18 January 2024 and for individuals 60 years of age and older on 26 March 2024. Additional applications are under review by other regulatory agencies around the world.

However, there are limited data on the safety and immunogenicity of RSVpreF in the Korean population, and further study of an older adult population is required for licensure in Korea.

Demonstration of safety and immunogenicity in this study may support licensure of the RSV vaccine in other populations with unmet medical need such as immunocompromised and high-risk adults, and infants via maternal vaccination.

After RSV natural infection, immunity is considered to be short-lived.[1,18] Currently, there is no licensed vaccine to prevent RSV disease in older adults, and there are no specific effective treatments for RSV in Korea. Most people infected with RSV recover within 1 to 2 weeks, but it can cause pneumonia in older or immunocompromised individuals, which may require hospitalization.[19] The only available prophylactic measure in Korea is a monoclonal antibody, which is limited to use in high-risk preterm infants and children under 2 years of age.[20] Therefore, there is an important unmet medical need to develop an effective vaccine to boost the immune response sufficiently to protect older adults against RSV disease in Korea.

Given the significant unmet medical need in Korea and the efficacy and safety of RSVpreF demonstrated in global studies, this study will be conducted to evaluate the safety, tolerability, and immunogenicity of RSVpreF in Korean older adults to support a licensure application in Korea.

2.2. Background

The vaccine investigated in this study is a bivalent RSV prefusion F subunit vaccine (RSVpreF) developed by Pfizer. The RSV F glycoprotein facilitates fusion of the virion and host cell membrane through a dramatic transition from an unstable but highly immunogenic prefusion conformation to the more stable postfusion state.[21] Preclinical studies show that prefusion F elicits much higher neutralizing antibody titers than postfusion F and that the most potent neutralizing antibodies from postinfection human sera target the prefusion form.[22] RSVpreF is composed of engineered, stabilized, trimeric, prefusion F glycoproteins matching the 2 subgroups (A and B) to help ensure the broadest coverage against RSV illness.

Pfizer's Phase 1 and 2 studies demonstrated proof that RSVpreF elicits robust neutralizing antibodies in adults that persisted for at least 12 months after vaccination (Studies C3671001 and C3671002)[23,24] and that a single 120-µg dose of RSVpreF had a 100% observed efficacy against qRT-PCR–confirmed symptomatic RSV infection in a human challenge model (Study WI257521).[25]

Proof that the vaccine is efficacious in preventing LRTI-RSV in older adults ≥60 years of age was demonstrated in a Phase 3 study (Study C3671013).[26] In the primary analysis, protection against LRTI-RSV defined by 2 or more symptoms demonstrated a 66.7% VE. A VE of 85.7% was observed in participants with the primary endpoint of LRTI-RSV defined by 3 or more RSV-associated symptoms. Additionally, the C3671008 Phase 3 maternal study recently demonstrated effectiveness in preventing severe LRTI-RSV in infants born to mothers who received RSVpreF.[27]

Even though there is no correlate for protection for RSV, RSV-neutralizing antibody titers correlate with the duration of passive infant protection from RSV and reduction in infant hospitalization due to RSV disease.[28,29] Additionally RSV-infected older adults have significantly lower serum RSV-neutralizing antibody titers and RSV-specific immunoglobulin G levels than uninfected age-matched controls.[30,31] Additional immune mechanisms beyond neutralization may also aid in protection, but the existing evidence supports an important role for serum neutralizing antibody titers in reducing the risk of RSV disease in older adults.

2.2.1. Clinical Overview

The older adult program includes 2 Phase 1/2 studies, 3 Phase 3 studies, and a Phase 2a human challenge study.[32]

- Study C3671001 (NCT03529773) is a completed Phase 1/2 study in 1235 healthy adults in 2 age groups—18 through 49 and 50 through 85 years of age—who received 1 of 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 NT GMFRs were high across all study arms, ranging from 9 through 13 from before vaccination to 1 month after vaccination and from 3 through 4 from before vaccination to 12 months after vaccination for RSV A and RSV B, respectively. 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 study intervention.[23]

- Study C3671002 (NCT03572062) is a completed Phase 1/2 study in 317 older adults 65 through 85 years of age. The primary cohort evaluated 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg), with $Al(OH)_3$ or $CpG/Al(OH)_3$, or placebo, given as a single dose concomitantly with SIIV; the Month 0 and Month 2 cohorts received either RSVpreF (240 µg) with $CpG/Al(OH)_3$ or placebo, given without concomitant SIIV, on a schedule of 2 doses administered 2 months apart. For the primary cohort, 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) at 12 months after vaccination (GMFRs ranging from 2.1 to 3.5 and 2.2 to 4.3, respectively). For the Month 0 and Month 2 cohorts, no increase in GMTs was observed 1 month after Vaccination 2 (GMFRs of 0.9). All doses and formulations were safe and well tolerated.[24]

- A Phase 2a, randomized, double-blinded, placebo-controlled study to evaluate the safety, immunogenicity, and efficacy of RSVpreF in a virus challenge model in healthy adults (NCT04785612) was conducted by hVIVO in 70 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 were evaluated. The primary analysis of the human challenge study showed that a 120-µg dose of RSVpreF was well tolerated and had an acceptable safety profile. The completed study demonstrated 100% efficacy of RSVpreF against RT-PCR–confirmed symptomatic respiratory infection in a mild-to-moderate disease model.[25]

- Study C3671006 (NCT05301322) is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blinded study. Approximately 1400 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 with a 120-µg dose of RSVpreF coadministered with SIIV were noninferior to the immune responses when these products were administered 4 weeks apart. The safety and tolerability of RSVpreF were also examined. Results demonstrated NI of the RSVpreF and SIIV immune responses when RSVpreF was coadministered with SIIV. The results of this study support the acceptability of coadministration of RSVpreF and SIIV in an older adult population.

- Study C3671013 (NCT05035212) is an ongoing Phase 3, multicenter, randomized, double-blinded, placebo-controlled study to assess the safety, immunogenicity, and efficacy of Pfizer's RSVpreF in the prevention of LRTI-RSV in adults 60 years of age and older. Both healthy adults and adults with stable chronic cardiopulmonary conditions are included. Approximately 15% of the enrolled participants have stable chronic cardiopulmonary conditions such as COPD, asthma, or CHF. The study enrolled over 37,000 participants, randomized to receive either RSVpreF or placebo in a 1:1 ratio. This is an event-driven study with a target of 59 first episodes of evaluable LRTI-RSV cases. Interim analysis results (data cutoff, 14 July 2022) showed protection against LRTI-RSV defined by 2 or more symptoms and a demonstrated VE of 66.7%. A VE of 85.7% was observed in participants with the primary endpoint of LRTI-RSV defined by 3 or more RSV-associated symptoms.[26] The vaccine was well tolerated, with no safety concerns.[7] On 31 May 2023, the FDA approved RSVpreF (Abrysvo) for marketing for individuals 60 years of age and older in the US.[33] On 23 August 2023, RSVpreF (Abrysvo) 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.[34]

  Revaccination Substudies A and B have been amended to the C3671013 protocol, each designed to evaluate the safety and immunogenicity of a second dose of RSVpreF when administered to participants after a dosing interval of either approximately 2 years (Substudy A) or approximately 1 year (Substudy B). A total of at least 800 but up to 900 participants who received RSVpreF in the efficacy study will be randomized in

Substudy A in a 1:1 ratio to receive RSVpreF or placebo. Up to 200 participants who received RSVpreF in the efficacy study will be randomized in Substudy B in a 1:1 ratio to receive RSVpreF or placebo. In both Substudy A and Substudy B, there are 5 scheduled study visits: Day 1 and 1 month, 6 months, 12 months, and 18 months after revaccination. Serum samples collected at all 5 visits will be assayed for RSV A and RSV B serum NTs. Safety assessments include immediate AEs within 30 minutes after each vaccination, local reactions and systemic events within 7 days after each vaccination, AEs until 1 month after revaccination, and AESIs, NDCMCs, and SAEs from signing of the ICD throughout substudy participation.

- Study C3671014 (NCT05096208) is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blinded, 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 each of the 3 manufactured RSVpreF lots 1 month after vaccination were equivalent, and that the 120-µg dose of RSVpreF was well tolerated and had an acceptable safety profile.

- Study C3671023 (NCT05842967) is an ongoing Phase 3 study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults at high risk of severe RSV disease in 2 distinct patient populations:

  - Substudy A is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of 120 µg RSVpreF in adults 18 to <60 years of age considered to be at high risk of RSV disease due to certain chronic medical conditions.

  - Substudy B is a Phase 3, single-arm, open-label, multicenter study that will assess the safety, tolerability, and immunogenicity of 120 µg RSVpreF in immunocompromised adults.

2.3. Benefit/Risk Assessment

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. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RSVpreF		
Pfizer has identified the most common risks for RSVpreF as local reactions such as injection site redness, injection site swelling, and injection site pain, and systemic events such as fatigue, headache, diarrhea, joint pain, nausea, vomiting, muscle pain, and fever. GBS has been identified as a potential risk for RSVpreF. Other events of interest include atrial fibrillation and polyneuropathy. 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.[35] 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 were 2 cases of GBS or its variants with a plausible temporal relationship with vaccination among >18,000 individuals who received RSVpreF. Both cases had confounding factors or alternative etiology. In Study C3671013, conducted in adults 60 years of age and older, there was a nonsignificant numerical imbalance in the number of cases of atrial fibrillation reported for individuals who received RSVpreF compared to individuals who received placebo. Most of the participants who had atrial fibrillation and received RSVpreF had a preexisting medical history of atrial fibrillation and/or cardiac disease.[36]	• 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 to determine if an unscheduled visit is required to be conducted per protocol. • Individuals with prior history of any subtype of GBS of any etiology will be excluded from study participation. • All study participants will be observed for at least 30 minutes after vaccination. • AEs and SAEs will be collected at specified time points throughout the study. • Specific references to risks and events of interest are made within the ICD, with reporting instructions if a case is suspected.
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants enrolled may be:

- Receipt of an 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 study participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The study objectives, endpoints, and estimands are presented in Table 3.

Table 3. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety profile of RSVpreF when administered to Korean adults ≥60 years of age	• Local reactions (redness, swelling, and pain at the injection site) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) • AEs • SAEs • NDCMCs	In participants receiving the study intervention, the percentage of participants reporting: • Local reactions within 7 days after vaccination • Systemic events within 7 days after vaccination • AEs within 1 month after vaccination • SAEs throughout the study • NDCMCs throughout the study
Immunogenicity		
To describe the immune responses to RSV A and RSV B elicited by RSVpreF in Korean adults ≥60 years of age	• RSV A and RSV B serum NTs	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • GMT of NTs for RSV A and RSV B at each blood sampling visit • GMFR of NTs for RSV A and RSV B from before vaccination to 1 month after vaccination

Table 3. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
Immunogenicity		
To further describe the immune responses to RSV A and RSV B elicited by RSVpreF in Korean adults ≥60 years of age	• RSV A and RSV B serum NTs	Seroresponse[a] rate of NTs for RSV A and RSV B at 1 month after vaccination

a. Seroresponse is defined as a postvaccination NT ≥4 times the LLOQ if the baseline titer is below the LLOQ; or a ≥4-fold rise from baseline if the baseline titer is ≥ LLOQ.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blinded, placebo-controlled, multicenter trial to describe the safety, tolerability, and immunogenicity of bivalent RSVpreF in adults 60 years of age and older in Korea.

Approximately 360 study-eligible participants will be randomized to receive either the 120-µg dose of RSVpreF or placebo in a 2:1 ratio. Randomization will be stratified by 3 age groups (60 through 69, 70 through 79, and ≥80 years), with approximately 100 participants estimated to be enrolled in the 70- through 79-year and ≥80-year age strata combined. Due to recruitment conditions, the distribution of the 3 age strata may not exactly match with the age distribution in the global Phase 3 pivotal study. Study arms, blood draws, and safety assessment timings are presented below.

"Enrolled" is defined as a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to the study intervention.

Before any study-related procedures are performed, participants will sign an ICD. After screening and confirmation of eligibility, a prevaccination blood sample (~20 mL) will be collected for immunogenicity assessments and a single dose of study intervention (RSVpreF or placebo) will be administered. Participants will be observed for at least 30 minutes after receiving the study intervention.

Participants will report daily reactogenicity data using an electronic device. Prespecified local reaction and systemic event data will be collected in an e-diary during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). Reported Grade 3 and potential Grade 4 reactogenicity events will be assessed by the investigator or qualified person to determine unscheduled medical visit requirements.

Participants will return approximately 1 month later for a follow-up blood draw for immunogenicity assessments and collection of safety information. A telephone follow-up visit will be conducted approximately 1 week after vaccination to review reactogenicity and approximately 2 months after vaccination to collect safety information. The overall study duration for each participant will be approximately 2 months from signing of the ICD to the final visit.

For all participants, AEs will be collected from informed consent through 1 month following study intervention administration. SAEs, NDCMCs, and AESIs will be collected from informed consent throughout study participation.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the study rationale.

4.2.1. Rationale for Comparator

As there is currently no approved vaccine for the prevention of RSV disease in Korea, a placebo was selected as the comparator for this protocol.

4.2.2. Choice of Contraception/Barrier Requirements

The study intervention is approved by the US FDA and EMA for use for pregnant individuals and older adults without any contraceptive precautions. There is no suspicion of human teratogenicity based on the intended pharmacology.

4.3. Justification for Dose

The 120-µg dose, without any adjuvants, is the dose level that has been approved for use by the FDA and EMA and has been proven efficacious in other studies enrolling diverse populations, and therefore is expected to be efficacious in the Korean population in this study.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants 60 years of age or older at Visit 1.

   - Male participants able to father children must agree to use a highly effective method of contraception from the time of informed consent through at least 28 days after study intervention administration (see Section 10.3.1).

   - Female participants must not be of childbearing potential (see Section 10.3.3).

Disease Characteristics:

2. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infections with HIV, HCV, or HBV can be found in Appendix 6, Section 10.6.

3. Participants who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, frequent symptom assessment by mobile device application (e-diary), and other study procedures.

4. Participants who are ambulatory and live in the community, or in assisted-living or long-term care residential facilities that provide minimal assistance, such that the participant is primarily responsible for self-care and ADL.

Other Inclusion Criteria:

5. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. A confirmed diagnosis of RSV infection ≤180 days before study intervention administration.

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

3. Prior history of any subtype of GBS of any etiology.

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) or any related vaccine.

5. Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.

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

7. Any medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Individuals who receive chronic systemic treatment with immunosuppressive therapy (other than systemic corticosteroids meeting the criteria noted below), including cytotoxic agents, immunosuppressive monoclonal antibodies, or radiotherapy, eg, for cancer or an autoimmune disease, from 60 days before study intervention administration or planned receipt throughout the study.

   Note:

   - Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days from 28 days before study intervention.

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

9. Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration.

10. Previous vaccination with any licensed or investigational RSV vaccine, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

11. Previous administration with an investigational product (drug or vaccine) within 6 months prior to study intervention administration. Participation in other studies involving an investigational product (drug or vaccine) at any time during participation in this study.

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

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 3, Section 10.3.1) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

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 with a new participant number.

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

The following conditions may allow a participant to be randomized and assigned a study intervention once the condition(s) has/have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

1. Current febrile illness (temperature ≥38.0°C) or other acute illness within 48 hours before study intervention administration.

2. Receipt of any nonlive or recombinant vaccine within 14 days, or any live vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any nonstudy vaccine within 14 days after study intervention administration.

4. 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.

   Note: Systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified IMPs and NIMPs, 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.

- Placebo (lyophile match).

6.1. Study Intervention(s) Administered

Table 4. Study Interventions and Study Arms

	Study Intervention(s)	
Intervention Name	RSVpreF	Placebo
Type	Vaccine	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	RSV vaccine 120 µg/vial powder for solution for injection	Lyophile match/sterile water for injection
Unit Dose Strength(s)	120 µg	N/A
Administered Volume	0.5 mL (entire contents of PFS)	0.5 mL (entire contents of PFS)
Dosage Level(s)	120 µg	N/A
Route of Administration	IM	IM
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Storage Conditions	The lyophilized vaccine drug product and the diluent are stored at 2°C to 8°C. Vaccine drug product vials should be reconstituted only when ready for preparing the doses in a syringe. The prepared vaccine dose should be stored as directed by the administration manual. The reconstituted vaccine should be handled at ambient temperature and should not be frozen or refrigerated.	The lyophilized cake and the diluent are stored at 2°C to 8°C. Placebo vials should be reconstituted only when ready for preparing the doses in a syringe. The prepared placebo dose should be stored as directed by the administration manual. The reconstituted placebo should be handled at ambient temperature and should not be frozen or refrigerated.
Packaging and Labeling	RSVpreF is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Study intervention(s) will be labeled as per country requirements.	Placebo is supplied as a lyophilized white cake containing excipients but no active ingredients, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a PFS of sterile water diluent for injection (supplied). Study intervention(s) will be labeled as per country requirements.
SRSD	IB	IB
Study Arm(s)		
Arm Title	RSVpreF	Placebo
	Participants will receive 1 dose (0.5 mL) of RSVpreF 120 µg at Visit 1.	Participants will receive 1 dose (0.5 mL) of placebo at Visit 1.

6.1.1. Administration

Participants will receive 1 dose (0.5 mL) of study intervention (RSVpreF 120 µg or placebo) at Visit 1 (Day 1) in accordance with the study's SoA. The entire contents of the PFS (0.5 mL) are to be administered.

The study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, unless medical contraindicated, in which case the injection may be administered in the dominant arm.

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

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

Study intervention administration details will be recorded on the CRF.

Following administration of study intervention(s) at the site, participants will be observed for 30 minutes by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.1.2. Medical Devices

1. The medical devices provided for use in this study are a vial adapter and PFS.

   Note: The vial adapters are being deployed 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.

2. Instructions for medical device use are provided in the IPM.

3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the study personnel throughout the clinical investigation (see Section 8.4.9) 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.

9. 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 interventions 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.

Note: Vials are single-use.

6.3. Assignment to Study Intervention

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

Study interventions will be dispensed at the study visits summarized in the SoA.

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

6.4. Blinding

This is a double-blinded study, as the physical appearance of RSVpreF and placebo will not differ.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

Please refer to the IPM for further details.

6.4.3. Blinding of Sponsor Personnel

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

Sponsor staff assigned to support blind-breaking cases will be unblinded.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is

warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's study intervention assignment unless this could delay further management of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system. The contact information for the study medical monitor is documented in the Study Team Contact List located in the supporting study documentation.

6.5. Study Intervention Compliance

Participants will receive the study intervention directly from the investigator or designee, under medical supervision. The date and time of the administration will be recorded in the source documents and recorded in the CRF. The study intervention identification details and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required vaccine Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

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.

6.8. Treatment of Overdose

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

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

6.9. Prior and Concomitant Therapy

6.9.1. Prohibited Concomitant Vaccinations and Treatments

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per Section 7.2). Medications and vaccinations should not be withheld if required for a participant's medical care.

- Investigational vaccines other than RSV vaccines and investigational drugs are prohibited within 6 months prior to study intervention administration and thereafter during the course of the study.

- Previous vaccination with any licensed or nonstudy investigational RSV vaccines or receipt of these vaccines during the course of the study are prohibited.

- Nonstudy nonlive or recombinant vaccines other than RSV vaccines should not be given within 14 days before or after study intervention administration, unless medically necessary.

- Nonstudy live vaccines should not be given within 28 days before or after study intervention administration, unless medically necessary.

- Receipt of blood/plasma products or immunoglobulin should not be given within 60 days prior to study intervention administration through the Visit 3 blood draw.

  Note: Monoclonal antibodies with targeted mechanisms of action used in the management of chronic illnesses (eg, migraine headaches, osteoporosis) are permitted, provided they do not meet exclusion criterion 8.

- Receipt of chronic systemic treatment with known immunosuppressant medications, other than systemic corticosteroids meeting the criteria noted below, within 60 days prior to study intervention administration through the Visit 3 blood draw.

- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to study intervention administration through the Visit 3 blood draw.

- 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

- Nonstudy nonlive or recombinant licensed vaccines other than RSV vaccines may be given starting 14 days after study intervention administration (Day 15).
- Nonstudy live licensed vaccines may be given starting 28 days after study intervention administration (Day 29).
- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
- The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration is permitted during the participant's participation in the study.

6.9.3. Recording Nonstudy Vaccinations and Concomitant Medications

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

- Any nonstudy vaccinations received from 28 days prior to study intervention administration until the last study visit.
- Prohibited medications and treatments listed in Section 6.9.1 (with the exception of antipyretics and other pain medications to prevent symptoms), if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

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;
- Reactogenicity event;
- AE;
- Investigator/physician request;
- Protocol deviation;
- Participant request;
- Other.

If a participant withdraws from the study, they 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.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue active study participation (eg, biological sample collection) will remain in the study and must continue to be followed for protocol-specified safety follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants 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 specified study procedures and/or postvaccination safety follow-up, and entered on the appropriate CRF page.

In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

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

- Should the participant 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 age of each participant will be collected to critically evaluate the immune response and safety profile.

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.

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

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

8.1.1. Telehealth Visits

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

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

8.2. Efficacy and/or Immunogenicity Assessments

8.2.1. Blood Collection

Blood samples (approximately 20 mL per sample) will be collected from participants for immunogenicity testing as specified in the SoA. Blood samples will be collected from all participants at Visit 1 (prior to study vaccination) and Visit 3 (1 month after study vaccination) for antibody assessment. The total blood sampling volume for individual participants is approximately 40 mL.

Blood samples will be processed at the study site, where the serum will be extracted, frozen, and stored. The serum samples will then be shipped to the central laboratory for analysis.

Instructions for the collection and handling of blood and serum samples will be provided in the laboratory manual. The date and time of each sample will be recorded. The immunogenicity serum samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.2.2. RSV Vaccine Antibody Testing

RSV A– and RSV B–neutralizing antibody titers will be measured at each blood sampling time point.

Sample collection may be halted or discontinued upon notification by Pfizer. This includes discontinuing sampling in dosed participants who are no longer eligible for the study as well as discontinuation for groups of participants or all participants.

All serum sample assays will be performed by Pfizer and/or at a facility designated by Pfizer.

8.2.3. Biological Samples

Serum 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.

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

8.3. Safety Assessments

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

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

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

Participants will be observed for at least 30 minutes after vaccination and any acute reactions occurring during the first 30 minutes after administration of the study intervention will be recorded on the CRF.

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. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Table 5, Table 6, and Table 7.

Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A clinical assessment and physical examination will be performed at Visit 1, Visit 3, and unscheduled reactogenicity visits.

A physical examination should include vital signs (oral or tympanic or temporal artery temperature, heart rate, respiratory rate, and seated BP) and evaluation of any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; and lymph nodes.

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

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

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

8.3.3. Clinical Safety Laboratory Assessments

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

8.3.4. Electronic Diary for Reactogenicity

Participants will be required to complete a reactogenicity e-diary through an application installed on a provisioned device or on the personal device of the participant. They will be asked to monitor and record prespecified local reactions, systemic events, and temperature daily for 7 days or longer following vaccination, where Day 1 is the day of vaccination. Participants will receive reminders to complete the reactogenicity e-diary on a daily basis, starting on the day of study intervention administration (Day 1) through Day 7, or longer if there are ongoing symptoms.

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

Data on local reactions, systemic events, and temperature recorded in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred

electronically to Pfizer for analysis and reporting. These data do not need to be recorded by the investigator in the CRF, except for the following conditions:

- Grade 4 local reactions will be collected in the CRF.
- Any local reactions or systemic events occurring within the first 30 minutes after study vaccination must be recorded on the CRF. The time of onset (relative to vaccination) must be recorded.
- If a participant withdraws because of prespecified event(s) recorded in the e-diary, the event(s) should be recorded on the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.
- The investigator or designee must obtain stop dates for any symptoms ongoing on the last day, from Day 7 onwards until resolution. The stop dates should be documented in the source documents and the information entered in the CRF.

Investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate participant compliance and as part of the ongoing safety review.

All provisioned e-diary devices must be collected per the study 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 volunteers enrolled in preventive vaccine clinical trials.[35]

8.3.4.2. Local Reactions

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

Redness and swelling will be measured by the participant and recorded in measuring device units (range: 1 to 21; an entry in the e-diary of 21 will be denoted as ≥21), and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

If a severe (Grade 3) local reaction 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 a qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. A Grade 4 local reaction will be collected on the CRF.

If a local reaction persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator or the study staff. The investigator will enter this additional information in the participant's source notes and CRF.

Table 5. Grading Scale for Local Reactions

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4[a]
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis
Pain (at the injection site)	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. Grade 4 local reactions will be collected on the CRF and assessed by the investigator or qualified designee.

8.3.4.3. Systemic Events

Following vaccination (where Day 1 is the day of vaccination), participants will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain, and to record the symptoms in the e-diary or appropriate device daily. The systemic symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

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

Further, if a systemic event persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator or the study staff. The investigator will enter this additional information in the participant's source notes and CRF.

Table 6. Grading Scale for Systemic Events

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4[a]
Fatigue (= tiredness in e-diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe nausea
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
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, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. Grade 4 systemic events will be collected on the CRF and assessed by the investigator or qualified designee.

8.3.4.4. Temperature and Fever Assessment

A digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected daily for 7 days or longer following vaccination (where Day 1 is the day of vaccination).

Fever is defined as an oral temperature of ≥38.0°C. The highest temperature for each day will be recorded in the e-diary, where possible. Temperature will be measured and recorded to 1 decimal place.

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

If a fever of >38.9°C is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.

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

Table 7. Ranges for Fever

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

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

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 10.5. 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 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 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 4. At Visit 4 (2-month follow-up), the participant will be contacted by telephone to inquire about SAEs, including hospitalizations, NDCMCs, and AESIs since Visit 3.

- Nonserious AEs will be collected from informed consent through 1 month following study intervention administration (Visit 3).
- SAEs, including hospitalizations, NDCMCs, and AESIs will be collected from informed consent through the last study visit (Visit 4).

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 the study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported via PSSA or using the Vaccine SAE Report 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 concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form or, if applicable, via PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Report Form or, if applicable, via PSSA, 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.

If a participant begins a new therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. A switch to a commercially available version of the study intervention is considered as a new therapy for the purposes of SAE reporting.

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 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 male participant who is receiving or has discontinued the study intervention inseminates a female partner.
- A female participant is found to be pregnant while receiving or after discontinuing the study intervention.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to the 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 needlestick injury, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by needlestick injury, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report the 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 an EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety via PSSA or using the Vaccine SAE Report 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 end of study.
- If an EDP occurs in the setting of environmental exposure, the investigator must report this information to Pfizer Safety using the Vaccine SAE Report Form and an 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 report 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 report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, or a terminated fetus), 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 nonparticipant is found to be breastfeeding while being exposed or having been exposed to the study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by needlestick injury, inhalation, or skin contact.

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

The following events are considered as AESIs:

- Diagnosis of GBS;
- Diagnosis of acute polyneuropathy without an underlying etiology;
- Diagnosis of atrial fibrillation.

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 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 Report Form.

8.4.8.1. Lack of Efficacy

This section is not applicable for these cohorts, 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 Section 10.5.3. 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 Sections 8.4.1 through 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.

Refer to Section 10.5.4 for instructions for documenting and reporting medical device deficiencies.

8.4.9.2. Regulatory Reporting Requirements for Device Deficiencies

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

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

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

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

8.4.10. Medication Errors

Medication 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.

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form or via PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.

8.9. Health Economics

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

8.10. Study Procedures

8.10.1. Visit 1 (Day 1 – Vaccination)

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

The investigator or their designee will also sign and date the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent 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 study intervention are conducted prior to study vaccination.

- Obtain written informed consent from the participant before performing any study-specific procedures.
- Assign a single participant identifier using the IRT system.
- Obtain and record the participant demography (including complete date of birth [DD/MMM/YYYY], sex, race, racial designation, and ethnicity). The age of each participant will be collected to critically evaluate the immune response and safety profile.

- Obtain and record significant medical history, including but not limited to, heart disease, lung disease, asthma, diabetes mellitus, liver disease, and renal disease.
- Obtain and record current/former tobacco usage.
- Perform a clinical assessment and physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure weight and height.
- Obtain details of any nonstudy vaccinations as described in Section 6.9.3.
- Obtain details of prohibited medications and treatments as described in Section 6.9.1.
- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.
- Discuss contraceptive use, if applicable, as described in Section 10.3.1.
- Measure and record prevaccination temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention kit number using the IRT system. Refer to the IRT manual for further instructions on this process.
- Prior to vaccination, collect a blood sample of approximately 20 mL for immunogenicity assessment.
- The qualified site staff member(s) will prepare and administer a single-vial 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 instructions on this procedure.
- Site staff must observe the participant for any acute reactions for at least 30 minutes after study intervention administration. Record any acute reactions in the participant's source documents, on the CRF, and on the Vaccine SAE Report Form or PSSA as applicable. All acute reactions must have the time of onset (relative to time of vaccination) recorded in the CRF.
- Issue the participant a measuring device and a digital thermometer and provide instructions on their use.

- Explain the e-diary technologies available for this study and assist the participant in downloading the study application onto their own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, or longer, until any symptoms that are ongoing are resolved, with Day 1 being the day of vaccination.
- Ask the participant 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 (Section 8.10.5).
    - Fever ≥39.0°C.
    - Redness or swelling at the injection site measuring >20 measuring device units.
    - Severe pain at the injection site.
    - Any severe systemic event.
- Remind the participant that study staff may contact them to obtain additional information on symptoms entered into the e-diary until they resolve.
- Remind participants to inform the study staff of any illnesses or medical events (eg, healthcare visits or hospitalization) that occur for the duration of the trial as described in Section 8.3.4 and Section 10.5.
- Remind the participant to bring the e-diary to the next visit.
- Record AE, NDCMCs, SAEs, and AESIs as described in Section 8.4 and Section 10.2.
- Schedule an appointment for the participant to return for the 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 e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.10.2. Visit 2 (1-Week Follow-Up)

- Contact the participant by telephone.
- Review the participant's e-diary data and record the assessment in the CRF. Assess compliance, record any medically attended events (including hospitalizations), and collect stop dates of any symptoms ongoing on the last day of the e-diary collection period in the CRF. For symptoms still ongoing, continue to follow up until resolution and document and record stop dates in the CRF.
- Remind the participant to bring the e-diary to the next visit.
- Obtain details of any nonstudy vaccinations and prohibited medications and treatments as described in Section 6.9.1.
- Record AE, NDCMCs, SAEs, and AESIs as described in Section 8.4 and Section 10.2.
- Remind participants to inform the study staff of any illnesses or medical events (eg, healthcare visits or hospitalization) that occur for the duration of the trial as described in Section 8.3.4 and Section 10.5.
- If appropriate, discuss contraceptive use as described in Section 10.3.1.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.3. Visit 3 (1-Month Follow-Up)

- Perform a clinical assessment and physical examination and record any findings in the source documents and, if the findings are clinically significant and meet the definition of an AE or SAE, record them on the CRF and according to the processes in Section 8.4.1 to Section 8.4.3.
- Obtain details of any nonstudy vaccinations and prohibited medications and treatments as described in Section 6.9.1.
- Collect a blood sample of approximately 20 mL for antibody assessment.
- Review ongoing reactogenicity e-diary symptoms reported as present on the last day of the e-diary collection period and obtain stop dates. Record stop dates in the CRF if required. Any ongoing reactions must be assessed at the next contact.
- Ensure that all data have been transferred from the e-diary prior to deactivating the application.

- Collect the participant's e-diary provisioned device or assist the participant with removing the study application from their personal device.
- Record AEs, AESIs, NDCMCs, and SAEs as described in Section 8.4 and Section 10.2.
- If appropriate, discuss contraceptive use as described in Section 10.3.1.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.4. Visit 4 (2-Month Follow-Up)

- Contact the participant by telephone.
- Obtain details of any nonstudy vaccinations and prohibited medications and treatments as described in Section 6.9.1.
- Review ongoing reactogenicity e-diary symptoms reported as present on the last day of the e-diary collection period and obtain stop dates. Record stop dates in the CRF if required.
- Record SAEs, NDCMCs, and AESIs as described in Section 8.4 and Section 10.2.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.5. Unscheduled Reactogenicity Visit

Phone Contact

If the participant reports 1 or more of the following, a phone contact **must** occur as soon as possible between the participant and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled reactogenicity visit is required, including:

- Fever ≥39.0°C,
- Redness at the injection site on the arm in which the study intervention was administered measuring >20 measuring device units (>10.0 cm),
- Swelling at the injection site on the arm in which the study intervention was administered measuring >20 measuring device units (>10.0 cm),
- Severe injection site pain in the arm in which the study intervention was administered,
- Any severe systemic event.

If a suspected Grade 4 local reaction (Section 8.3.4.2), systemic event (Section 8.3.4.3), or fever (Section 8.3.4.4) 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 or referral to a healthcare facility should be scheduled as soon as possible to assess the extent of the reaction, unless:

- The participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator or appropriate designee determines that the visit is not required, or
- The investigator or appropriate designee confirmed a severe reactogenicity assessment via medical records and/or telehealth assessment.

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

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

Site Visit Procedures

If an unscheduled reactogenicity site visit is required, reactogenicity events should be assessed by the investigator or a medically qualified member of the site staff such as a study physician or a study nurse, as applicable to the investigator's local practice or healthcare facility. Perform a clinical assessment and physical examination:

- Measure temperature (oral, tympanic, or temporal artery),
- Measure BP (seated),
- Measure heart rate,
- Measure respiratory rate,
- Using a ruler or tape measure, measure the minimum and maximum diameters of redness (if present) on the arm in which the study intervention was administered,
- Using a ruler or tape measure, measure the minimum and maximum diameters of swelling (if present) on the arm in which the study intervention was administered,
- Assess if necrosis is present at the injection site on the arm in which the study intervention was administered,

- Assess if any exfoliative dermatitis is present at the injection site on the arm in which the study intervention was administered,
- Assess any injection site pain that is present in the arm in which the study intervention was administered in accordance with the reactogenicity grading scale provided in Section 8.3.4.2,
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 8.3.4.3.

Additionally,

- Record any nonstudy vaccinations and prohibited medications and treatments as described in Section 6.9.1,
- Ask the participant if he/she attended an emergency room visit or was hospitalized for management of postvaccination local reactions or systemic events,
- Record AEs, AESIs, NDCMCs, and SAEs as described in Section 8.4 and Section 10.2,
- Complete the participant's source documents,
- Complete the CRFs.

The study staff may contact the participant to obtain additional information on events entered into the e-diary until they resolve.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined 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 Hypotheses

This is a descriptive study without any hypothesis testing.

9.2. Analysis Sets

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

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

Defined Analysis Set	Description
Evaluable immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Receive the study intervention to which they were randomized; • Have the 1-month postvaccination blood collection visit 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 were randomized and had at least 1 valid and determinate assay result after receiving the 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

Unless stated otherwise, “vaccine group” in this section refers to the study intervention group. 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 received. Missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the mITT immunogenicity population if there is a large enough difference in sample size between the mITT immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing immunogenicity results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for binary variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[37]

The 95% CI for the difference in the proportions will be computed using the Miettinen and Nurminen method.[38] The 95% CI will be presented in terms of percentage.

9.3.1.2. Analyses for Continuous Data

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

CIs for the mean of the continuous variables will be constructed by the standard method based on the Student t distribution.

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 log e scale based on the t distribution, and then exponentiating the results.

9.3.1.2.2. Geometric Mean Fold Rises

Fold rises are defined as ratios of the results after vaccination to the results before vaccination. The calculations of fold rises are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. 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 8. Primary Endpoint Analyses

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. Local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, nausea, fatigue, 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% CIs (Section 9.3.1.1). • AEs (including AESIs), NDCMCs, and SAEs will be categorized according to MedDRA terms. All AEs within 1 month after study intervention administration, and all AESIs, NDCMCs, and SAEs throughout the study will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CIs for each vaccine group (Section 9.3.1.1). • A 3-tier approach will be used to summarize AEs. (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan and described in detail in the SAP. (2) Tier 2 events are considered "relatively common" events; a MedDRA preferred term is defined as a Tier 2 event if at least 4 participants in at least 1 vaccine group report the event. (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events.

Table 8. Primary Endpoint Analyses

Endpoint	Statistical Analysis Methods
	• For Tier 1 and Tier 2 events, the 95% CIs for the difference in the percentage of participants reporting the events between the RSVpreF group and the placebo group will be calculated using the test statistic proposed by Miettinen and Nurminen. In addition, for Tier 1 events, the p-values will be presented for the difference between groups in the percentage of participants reporting the events. For Tier 3 events, counts and percentages for each vaccine group will be provided.
Immunogenicity	• GMTs and their associated 95% CIs will be descriptively summarized, by vaccine group, for both RSV A and RSV B at each blood sampling visit (Section 9.3.1.2.1). • GMFRs of NTs from before vaccination to 1 month after vaccination will be descriptively summarized with 95% CIs, by vaccine group, for both RSV A and RSV B (Section 9.3.1.2.2). • Empirical RCDCs will be provided for RSV A and RSV B NTs at 1 month after vaccination (Section 9.3.1.2.3).

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

Endpoint	Statistical Analysis Methods
Immunogenicity	• RSV A NT and RSV B NT seroresponse rate at 1 month after vaccination will be provided with the associated Clopper-Pearson 2-sided 95% CIs (Section 9.3.1.1). • Immunogenicity data may be further summarized by age stratum.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

9.4. Interim Analyses

No interim analysis is planned. One final analysis will be performed when all immunogenicity and safety data are cleaned.

9.5. Sample Size Determination

As this study is not a hypothesis-testing study, the sample size was not based on study power for success.

It is expected that 240 participants will receive RSVpreF, with a total of 360 participants randomized in a 2:1 ratio. Assuming an ~10% nonevaluable rate, ~210 participants in the RSVpreF group will be assessed for immunogenicity.

Based on historical data, the GMFR at 1 month after vaccination with RSVpreF was ~10 (or 2.3 in the log e scale) among participants ≥60 years of age. With 210 participants expected to be evaluable after receiving RSVpreF, there is a 2.4% and 5% possibility of observing an LB of the 95% CI for the GMFR <7.5 for RSV A and RSV B, respectively.

Antigen/ Strain	Common SD of Fold Rise (Log e Scale)[a]	Probability of Observing an LB of 95% CI for the GMFR <7.5 (or 2.0 in the Log e Scale)
RSV A	1.1	2.4%
RSV B	1.2	5.0%

a. Based on Study C3671013.

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 Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site 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 not use an EDMC.

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 re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), 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 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 sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the supporting study documentation.

Participants are provided with a Pfizer study information card at the time of informed consent, which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study ID number, and (c) PI contact information.

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

10.2.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either 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 using the Vaccine SAE Report Form or, if applicable, via PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Report Form/PSSA to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety using the Vaccine SAE Report Form or, if applicable, via PSSA.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Report Form or, if applicable, via PSSA, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Report 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 Report 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between 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 Report Form/PSSA and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other 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 (eg, eSAE or PSSA). • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken 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 Report Form
• Facsimile transmission of the Vaccine SAE Report Form is one of the preferred methods 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 Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

10.2.5. Definition of NDCMC

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

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom when having sexual intercourse with a WOCBP who is not currently pregnant.

10.3.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not a WOCBP (see definitions below in Section 10.3.3).

10.3.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are <u>not</u> considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
  - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.4. Contraception Methods

Not applicable for female participants.

Refer to Section 10.3.1 for male participants.

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, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation 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: 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).

10.5.1. 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.

10.5.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 2, Section 10.2.2.
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US 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.

10.5.3. 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.

10.5.4. 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. • If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF. • The investigator will notify the sponsor study team by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency. • The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group. • If the investigator 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. All relevant details related to the role of the device

in regard to the SAE must be included in the Vaccine SAE Report Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

    - For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

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

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB in their assessment.

- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

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

Follow-Up of Medical Device Deficiency

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the sponsor study team.
- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 2.

10.6. Appendix 6: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV infection with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation

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
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
ARI	acute respiratory illness
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BP	blood pressure
CAP	community-acquired pneumonia
CBER	Center for Biologics Evaluation and Research (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
CpG	cytosine phosphate guanine
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram or electrocardiography
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eICD	electronic informed consent document
EMA	European Medicines Agency
eSAE	electronic serious adverse event

Abbreviation	Term
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMT	geometric mean titer
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCAP	healthcare-associated pneumonia
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRSV	human respiratory syncytial virus
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
ILI	influenza-like illness
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	Internet Protocol
IPAL	investigational product accountability log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
LB	lower bound
LFT	liver function test
LLOQ	lower limit of quantitation
log e	natural logarithm
LRTD	lower respiratory tract disease

Abbreviation	Term
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety (Republic of Korea)
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
mITT	modified intent-to-treat
MQI	medically qualified individual
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NIMP	noninvestigational medicinal product
NT	neutralizing titer
PACL	protocol administrative change letter
PFS	prefilled syringe
PI	principal investigator
PSSA	Pfizer's Serious AE Submission Assistant
PT	prothrombin time
qRT-PCR	quantitative reverse transcription–polymerase chain reaction
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RT-PCR	reverse transcription–polymerase chain reaction
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
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
TBA	to be announced
T bili	total bilirubin
UADE	unanticipated adverse device effect

Abbreviation	Term
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States prescribing information
VE	vaccine efficacy
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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Document Approval Record

Document Name:	C3671053 Clinical Protocol Amendment 1, Clean Copy, 17Mar2025
Document Title:	A PHASE 3 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN OLDER ADULTS IN KOREA

Signed By:	Date(GMT)	Signing Capacity
PPD	17-Mar-2025 15:29:53	Final Approval
PPD	17-Mar-2025 16:38:51	Final Approval