A PHASE 3 PROTOCOL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN ADULTS AT HIGH RISK OF SEVERE RSV DISEASE

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Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Phase 3 Protocol to Evaluate the Safety, Tolerability, and Immunogenicity of RSVpreF in Adults at High Risk of Severe RSV Disease

Document History

Document	Version Date
Amendment 1	18 Aug 2023
Original protocol	07 Mar 2023

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

Protocol Amendment Summary of Changes Table

Amendment 1 (18 August 2023)

Overall Rationale for the Amendment:

To increase the sample size in Substudy A by an additional 150 participants and add an additional estimand for the primary immunogenicity objective. Updated corresponding details in the Substudy A objectives and statistical methods sections. Surveillance of defined AESIs added for both substudies.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Updated text with respect to increased recruitment to Substudy A.	To obtain data from an additional 150 individuals in Substudy A per feedback from FDA/CBER.	Section 1.1 Synopsis Section 4 Study Design Section 10.7.1.2 Schema: Substudy A Section 10.7.4 Study Design for Substudy A Section 10.7.9 Statistical Considerations for Substudy A
Added an additional estimand to the primary immunogenicity objective of Substudy A.	To determine the difference in seroresponse rate of RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF between participants in Study C3671023 and in C3671013.	Section 10.7.3 Objectives, Endpoints, and Estimands for Substudy A Section 10.7.4 Study Design for Substudy A Section 10.7.9 Statistical Considerations for Substudy A

Description of Change	Brief Rationale	Section # and Name
Added AESI surveillance through the end of study participation. Updated risk text with these events of interest.	Diagnosis of Guillain-Barre syndrome, acute polyneuropathy without an underlying etiology, atrial fibrillation, preterm delivery (delivery at <37 0/7 weeks' gestation), and hypertensive disorders of pregnancy are considered AESIs.	Section 8.4.8 Adverse Events of Special Interest Section 8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting Section 1.1 Synopsis Section 2.3.1 Risk Assessment Section 10.7.1.3 Schedule of Activities: Substudy A Section 10.7.4.1 Overall Design (Substudy A) Section 10.7.8.4 Substudy A Procedures Section 10.7.9.3.2 Primary Endpoint(s)/Estimands(s) Analysis (Substudy A) Section 10.8.1.3 Schedule of Activities: Substudy B Section 10.8.4.1 Overall Design (Substudy B) Section 10.8.8.4 Substudy B Procedures Section 10.8.9.3.2 Primary Endpoint(s)/Estimands(s) Analysis (Substudy B)
Clinicaltrials.gov reference and sponsor legal address added to the title page.	To update to reflect trial posting to clinicaltrials.gov.	Title page
Removed reference to "master" when describing the protocol.	Per CBER feedback on use of "master protocol" terminology.	Title and throughout the entire protocol
Nonsubstantial Modification(s)		
Updated the text with respect to the FDA approval of RSVpreF (Abrysvo™) for marketing in individuals 60 years of age and older in the US and approvals of prophylactic monoclonal antibodies for RSV.	To capture updated information on approvals for RSV vaccine and monoclonal antibodies.	Section 1.1 Synopsis Section 2 Introduction Section 7.2 Participant Discontinuation/Withdrawal From the Study Section 11 References
Updated text with respect to other trials within the Pfizer RSV program.	To capture updates on trial statuses and results.	Section 1.1 Synopsis Section 2.2.1 Clinical Overview
Added appendix providing guidance for potential participants with chronic stable HIV infection.	To provide further guidance for sites.	Section 10.6 Appendix 6: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV Infection Section 10.7.5.2 Exclusion Criteria (Substudy A)

Description of Change	Brief Rationale	Section # and Name
		Section 10.7.8.4.1 Visit 101 – Vaccination (Clinic, Day 1) (Substudy A Procedures) Section 10.8.5.2 Exclusion Criteria (Substudy B) Section 10.8.8.4.1 Visit 201 – Vaccination 1 (Clinic, Day 1) (Substudy B Procedures)
Updated text for exclusion criteria, temporary delay criteria, and prohibited medication lists in Substudy A.	To provide further clarification to sites on which monoclonal antibodies and corticosteroids are excluded or require temporary delay. Details added regarding participants remaining in a temporary delay at the time of enrollment closure and actions to take if prohibited medications are taken.	Section 10.7.5.2 Exclusion Criteria Section 10.7.5.5 Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention Section 10.7.6.7 Prior and Concomitant Therapy for Substudy A
Updated text for exclusion criteria, temporary delay criteria, and prohibited medication lists in Substudy B.	To provide further clarification to sites on which monoclonal antibodies are excluded or require temporary delay. Details added regarding participants remaining in a temporary delay at the time of enrollment closure and actions to take if prohibited medications are taken.	Section 10.8.5.2 Exclusion Criteria Section 10.8.5.5 Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention Section 10.8.6.7 Prior and Concomitant Therapy for Substudy A
Added check marks for kit allocation via the IRT and e-diary training for the second study intervention administration in Substudy B.	To align the protocol with processes carried out prior to the second administration of study intervention in Substudy B.	Section 10.8.1.3 Schedule of Activities: Substudy B Section 10.8.8.4.2 Visit 202 – Vaccination 2 (Clinic, 28 to 35 Days After Vaccination at Visit 201) (Substudy B Procedures)
Updated text to clarify respiratory rate at baseline, oversight and reporting of missed reactogenicity e-diary days, and blood sample discontinuation.	To align the protocol with activities and processes captured in other study documentation.	Section 1.3 Schedule of Activities Section 8 Study Assessments and Procedures Section 8.3.2 Vital Signs Section 8.3.4 Electronic Diary for Reactogenicity Section 9.3.1 General Considerations (Statistical Analyses) Section 10.7.1.3 Schedule of Activities: Substudy A Section 10.7.8.1.1 RSV Vaccine Antibody Testing (Substudy A)

Description of Change	Brief Rationale	Section # and Name
		Section 10.8.1.3 Schedule of Activities: Substudy B Section 10.8.8.1.1 RSV Vaccine Antibody Testing (Substudy B)
Added reference to PSSA for reporting of safety information to Pfizer Safety and edited text in line with current process.	To capture the reporting process to Pfizer Safety via PSSA.	Section 8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting Section 10.2 Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting
Removed risk related to the COVID-19 pandemic.	Change to pandemic status was declared in May 2023.	Section 1.1 Synopsis Section 2.3.1 Risk Assessment
Minor editorial changes.	Corrections or minor edits in line with amendment and template updates and/or to improve clarity and navigation throughout the document for sites.	All

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1. PROTOCOL SUMMARY

1.1. Synopsis

RSV is an important cause of severe respiratory disease associated with high morbidity and mortality in older adults ≥60 years of age and adults ≥18 years of age with underlying chronic medical conditions or who are immunocompromised. After RSV natural infection, there is only a relatively short duration of immunity. Currently, no specific effective treatments for RSV exist. Current treatments consist primarily of supportive care. On 31 May 2023, based on efficacy and safety data from the study in the older adult population (C3671013), the FDA approved RSVpreF (Abrysvo™) for marketing in individuals 60 years of age and older in the US. There is currently no licensed vaccine to prevent RSV infection in younger adults, and further studies are required for adults with weakened immune systems.

The only other available prophylactic measures are monoclonal antibodies, which are limited to use in infants and children up to 24 months of age. Therefore, there is an important unmet medical need to develop an effective vaccine to boost the immune response sufficiently to protect immunocompromised adults and adults under 60 years of age at high risk of severe RSV disease.

This is a Phase 3 study to evaluate the safety, tolerability, and immunogenicity of RSVpreF in adults at high risk of severe RSV disease and immunocompromised adults. Studying the safety, and/or tolerability, and/or immunogenicity of RSVpreF under a single protocol, rather than separate protocols, will allow an organized approach that can be easily adapted as different countries' licensure requirements are incorporated. This approach will be not only more expeditious to implement but also more readily understandable for investigational sites.

Protocol Title:

A Phase 3 Protocol to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults at High Risk of Severe RSV Disease

Brief Title:

A Phase 3 Protocol to Evaluate the Safety, Tolerability, and Immunogenicity of RSVpreF in Adults at High Risk of Severe RSV Disease

Regulatory Agency Identification Number(s):

US IND Number:	017931
EudraCT/EU CT Number:	Not Applicable
ClinicalTrials.gov ID:	NCT05842967
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C3671023
Phase:	3

Rationale:

Study C3671013 (NCT05035212) is an ongoing Phase 3 trial in ~45,000 participants designed to generate safety, immunogenicity, and efficacy data for Pfizer's RSVpreF vaccine candidate. Proof that the vaccine is efficacious in preventing LRTI caused by RSV in older adults (≥60 years of age) was demonstrated in this study. In the primary analysis, protection against LRTI-RSV defined by 2 or more symptoms demonstrated a 66.7% vaccine efficacy. Vaccine efficacy of 85.7% was observed in participants with the primary endpoint of LRTI-RSV defined by 3 or more RSV-associated symptoms. On 31 May 2023, based on efficacy and safety data from this study in the older adult population, the FDA approved RSVpreF (Abrysvo) for individuals 60 years of age and older in the US.

Study C3671013 enrolled participants ≥60 years of age who were healthy or had stable chronic medical conditions, including COPD, asthma, and CHF, but prohibited the enrollment of adults 18 through <60 years of age and all immunocompromised adults.

Given that individuals 18 through 60 years of age with high-risk medical conditions are at significant risk of morbidity and mortality due to RSV infection and given the severity of RSV disease observed in immunocompromised hosts 18 years of age and older, it is important that the safety and immune response to vaccination among this cohort are investigated. In order to obtain information regarding the safety and immunogenicity among high-risk participants, representative medical conditions (and their respective treatments) have been selected for the current study. Medical conditions and associated treatments have been selected on the basis of the substantial morbidity/mortality associated with RSV infection, feasible recruitment timelines, regulatory requirements, and the ability to generalize safety and immunogenicity results overall.

Objectives, Endpoints, and Estimands:

Please refer to the substudy appendices for the objectives, endpoints, and estimands of each substudy.

Overall Design:

This is a Phase 3 protocol that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults at high risk of severe RSV disease. Each substudy design is detailed separately, and these substudies may be conducted in parallel, as required by the clinical plan, within the framework of this protocol.

Substudy A Design

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

Approximately 675 participants ≥18 to <60 years of age considered at high risk of RSV disease due to certain chronic medical conditions, excluding immunocompromising conditions, will be randomized to receive a single 120-µg dose of RSVpreF or placebo in a 2:1 ratio. Enrollment will be monitored to help ensure distribution of vaccination across the age range. The duration of study participation for each participant will be 6 months, with 3 scheduled visits.

All participants will have blood drawn at baseline prior to vaccination and at 1 month after vaccination to assess immunogenicity. Immunogenicity elicited at 1 month after vaccination with RSVpreF in Substudy A will be bridged to the immunogenicity of participants 60 years of age and older in the C3671013 study, in which RSVpreF efficacy was demonstrated.

Local reaction and systemic event data will be collected in an e-diary for 7 days after study vaccination (Days 1 through 7, where Day 1 is the day of vaccination). Reported Grade 3 reactogenicity will be assessed by the study site to determine if an unscheduled visit is required.

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

Substudy B Design

This is a Phase 3, single-arm, open-label, multicenter study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in immunocompromised adults.

Approximately 200 immunocompromised adults ≥18 years of age will receive 2 120-µg doses of RSVpreF with an interval of 1 month. Approximately 100 participants will be ≥60 years of age and approximately 100 participants will be ≥18 to <60 years of age. Enrollment will be monitored to help ensure distribution of vaccination across the age ranges and underlying immunocompromising conditions. The duration of study participation for each participant will be 7 months, with 4 scheduled visits. All participants will have blood drawn at baseline prior to vaccination and at 1 month after (each) vaccination to assess immunogenicity.

Local reaction and systemic event data will be collected in an e-diary for 7 days after study vaccination (Days 1 through 7, where Day 1 is the day of vaccination). Reported Grade 3 reactogenicity will be assessed by the study site to determine if an unscheduled visit is required.

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

Number of Participants:

Substudy A: Approximately 675 participants will be enrolled in the study.

Substudy B: Approximately 200 participants will be enrolled in the study.

Note: **"Enrolled"** means a participant's agreement to participate in a clinical study following completion of the informed consent process. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity.

Study Population:

Please refer to the substudy appendices for the inclusion and exclusion criteria of each substudy.

Study Arms and Duration:

Please refer to the substudy appendices for the study arms and duration of each substudy.

Statistical Methods:

Please refer to the substudy appendices for the statistical methods of each substudy.

Ethical Considerations:

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

RSVpreF is an F glycoprotein subunit stabilized in the prefusion conformation, eliciting strong neutralizing antibodies as established in the adult studies and has already shown efficacy in preventing LRTI in older adults and severe LRTI in infants born to vaccinated mothers.

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

- Local reactions, such as injection site redness, injection site swelling, and injection site pain; systemic events, such as fatigue, headache, muscle pain, and joint pain; and fever.
- One case of Guillain-Barre syndrome and 1 case of Miller Fisher syndrome (both with a plausible temporal relationship with vaccination) were identified in Study C3671013 conducted in older adults 60 years of age and older.

The study procedure-related risks include:

- Venipuncture will be performed during the study.

1.2. Schema

Please refer to the substudy appendices for the schema of each study.

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. Based on review of data, at Pfizer's discretion, study visits, blood sample collection/analysis, or other procedures may be halted or discontinued if in the best interests of a participant (eg, should the participant be found to not meet certain eligibility criteria after administration of study intervention).

For the Substudy A SoA, refer to Section 10.7.1.3.

For the Substudy B SoA, refer to Section 10.8.1.3.

2. INTRODUCTION

Pfizer is currently developing a vaccine, RSVpreF, for the prevention of LRTI-RSV by protecting adults 60 years of age and older via direct immunization and maternal immunization during pregnancy. On 31 May 2023, based on efficacy and safety data from the study in the older adult population (C3671013), the FDA approved RSVpreF (Abrysvo™) for marketing in individuals 60 years of age and older in the US.[1]

RSV is a major cause of respiratory infection in all ages, which 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.

There are 2 antigenic variants of RSV, RSV A and RSV B, that cocirculate.[2] Like influenza, RSV infection typically 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.[3]

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. 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.[4] However younger

at-risk populations have been found to have significant sequelae from severe RSV disease, including ICU admission and mechanical ventilation. At-risk adults (18 years of age and older) include patients with cardiopulmonary or renal disease, and immunocompromised patients, including SOT and HSCT recipients, patients on chemotherapy treatment or immunomodulator drugs, and others.[5,6,7] In one study, with a mean age of 53.78 among HSCT and 55 among SOT recipients, the mortality rate from RSV-LRTI was 4.9% and 10.7% for HSCT and SOT recipients,[6] respectively, which is comparable to older adults.[8] Current epidemiology shows that RSV is responsible for approximately 60,000 to 160,000 hospitalizations and 6,000 to 13,000 deaths annually in US adults 65 years of age and older,[9,10,11,12] and 40,000 to 60,000 hospitalizations also occur among those <65 years of age annually, most of which would be among persons with chronic medical conditions.[9,12,13,14,15,16] Morbidity is significant among adults hospitalized with RSV disease, with 18% requiring intensive care, 31% needing home health services at discharge, and 26% dying within 1 year of hospitalization.[17]

In the US, RSV disease incidence rates in older adults are approximately half those of influenza, with variation year to year.[18] The incidence rate and risk for severe complications from RSV infection are higher among immunocompromised adults and those with chronic conditions (eg, cardiopulmonary or renal disease, hematological malignancies, receipt of chemotherapy, or HIV).[19,20] However, the burden of adult RSV disease is underestimated since RSV disease in adults is difficult to diagnose based on clinical signs and symptoms alone, testing for RSV is less common in older adults than in children, and even when testing is conducted, RSV infection is more difficult to detect with a single diagnostic specimen due to lower viral loads among adults.[21]

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, anemia concerns, and high cost, making vaccination a high priority.[20,22]

2.1. Study Rationale

RSV is an important cause of severe respiratory disease in older adults and adults ≥18 years of age with health conditions that put them at increased risk of severe RSV and/or complications and that are associated with a high rate of morbidity and mortality.[23,24]

Adults ≥18 years of age considered at high risk for severe RSV disease include*:

- Individuals who have chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus).
- Immunocompromised hosts.

*Risk factors are adapted from the CDC guidance on people at higher risk of influenza complications.[25]

Study C3671013 enrolled participants ≥60 years of age who were healthy or had stable chronic medical conditions, including COPD, asthma, and CHF, but prohibited the enrollment of adults ages 18 to <60 years of age and all immunocompromised adults. Limited data on safety and immunogenicity exist for adults 18 to <60 years of age with health conditions that place them at higher risk of RSV disease as well as immunocompromised individuals. On 31 May 2023, based on efficacy and safety data from the study in the older adult population (C3671013), the FDA approved RSVpreF (Abrysvo) for marketing in individuals 60 years of age and older in the US.[1] There is currently no licensed vaccine to prevent RSV infection in younger adults, and further studies are required for adults with weakened immune systems.

After RSV natural infection, immunity is considered to be short-lived.[2,26] Current treatments consist primarily of supportive care. The only other available prophylactic measures are monoclonal antibodies, which are limited to use in infants and children up to 24 months of age.[27,28,29] Therefore, there is an important unmet medical need to develop an effective vaccine to boost the immune response sufficiently to protect adults 18 years of age and older with underlying medical conditions, including an immunocompromised state, that put them at increased risk of severe RSV and/or complications against RSV disease.

Studying the safety, and/or tolerability, and/or immunogenicity of RSVpreF in adults at high risk of severe RSV disease and immunocompromised adults under a single protocol, rather than separate protocols, will allow an organized approach that can be easily adapted as different countries' licensure requirements are incorporated.

This approach will be not only more expeditious to implement but also more readily understandable for investigational sites.

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. 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. 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.

RSVpreF is being developed for 2 indications with 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.

Pfizer's Phase 1 and 2 studies demonstrated proof that RSVpreF elicits robust neutralizing antibodies in adults that persisted for at least 12 months after vaccination (Studies C3671001 and C3671002) and that a single 120-µg dose of RSVpreF had 100% observed efficacy against RT-PCR–confirmed symptomatic RSV infection in a human challenge model (Study WI257521). Proof that the vaccine is efficacious in preventing LRTI caused by RSV in older adults ≥ 60 years of age was demonstrated in a Phase 3 study (Study C3671013). In the primary analysis, protection against LRTI-RSV defined by 2 or more symptoms demonstrated a 66.7% vaccine efficacy. A vaccine efficacy 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 RSV-associated severe LRTI in infants born to mothers who received RSVpreF.

2.2.1. Clinical Overview

Adult Program Studies

The older adult program includes 2 Phase 1/2 studies, 3 Phase 3 studies, and a Phase 2a human challenge study.[30] The pediatric program has recently initiated with the Phase 1 portion of a Phase 1/2/3 study (C3671016).

- In the Phase 1/2 C3671001 study (NCT03529773), 1233 healthy adults 18 through 49 and 50 through 85 years of age received the 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg), with or without $Al(OH)_3$, or placebo, administered with or without concomitant influenza vaccine. The results have shown that the vaccine was well tolerated and immunogenic in both age groups. RSVpreF elicited robust neutralizing responses against RSV A and RSV B 1 month after vaccination for both age groups across all vaccine dose levels and formulations; these responses remained high through the 12 months after vaccination. In 616 vaccinated participants in the 50 through 85 years age group, RSV NT50 GMFRs were high across all 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 for RSV A and RSV B. RSVpreF was safe and well tolerated when administered alone or with SIIV, with no major differences observed across all dose levels and formulations. Most reported local reactions or systemic events were mild or moderate in severity. The proportions of participants reporting AEs were generally similar across RSVpreF groups, and no SAEs were considered related to the study intervention.

- In the Phase 1/2 C3671002 study (NCT03572062) in 250 older adults 65 through 85 years of age, 3 dose levels of RSVpreF with $Al(OH)_3$, or $CpG/Al(OH)_3$ (60 µg, 120 µg, and 240 µg), given as a single dose or on a schedule of 2 doses administered 2 months apart were studied. 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). No increase in GMTs was observed 1 month after Vaccination 2 (GMFR of 0.9). All doses and formulations were safe and well tolerated.

- Study C3671014 (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 ratio of neutralizing GMTs for each of the 3 manufactured RSVpreF lots 1 month after vaccination are equivalent and that the 120-µg dose of RSVpreF is well tolerated and has an acceptable safety profile.

- 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 healthy participants 18 to 50 years of age. Participants received a single dose of either 120 µg RSVpreF or placebo and 4 weeks later underwent intranasal challenge with RSV-A Memphis 37b virus. The immunogenicity and efficacy of RSVpreF vaccination on virus replication, clinical symptoms, and incidence of symptomatic RSV infection were evaluated. The primary analysis of the human challenge study showed that a 120-µg dose of RSVpreF is well tolerated and has an acceptable safety profile. The study has demonstrated 100% efficacy of RSVpreF against RT-PCR–confirmed symptomatic respiratory infection in a mild-to-moderate disease model.

- 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 10% of participants with stable chronic cardiopulmonary conditions, such as COPD, asthma, or CHF, have been enrolled. The study enrolled over 37,000 participants, randomized to receive RSVpreF or placebo in a 1:1 ratio. This is an event-driven study with a target of 59 first episodes of evaluable LRTI-RSV cases. Interim analysis results in August 2022 showed protection against LRTI-RSV defined by 2 or more symptoms and a demonstrated vaccine efficacy of 66.7%. A vaccine efficacy of 85.7% was observed in participants with the primary endpoint of LRTI-RSV defined by 3 or more RSV-associated symptoms. The vaccine was well tolerated, with no safety concerns.[30,31] On 31 May 2023, the FDA approved RSVpreF (Abrysvo) for marketing in individuals 60 years of age and older in the US.[1]

- Study C3671006 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 RSVpreF dose coadministered with SIIV were noninferior to the immune responses when these products were administered 4 weeks apart. The safety and tolerability of RSVpreF were also examined. Results demonstrated noninferiority of the RSVpreF and SIIV immune responses when RSVpreF was coadministered with SIIV. The results of this study support the acceptability of coadministration of RSVpreF and SIIV in an older adult population.

- C3671016 is a Phase 1/2/3 study in participants 2 to <18 years of age at high risk of RSV disease initiated in June 2023. The study consists of 2 phases: Phase 1 and Phase 2/3. Phase 1 is an open-label, age descending, dose-finding study and Phase 2/3 is a placebo-controlled, randomized, double-blinded study to evaluate the safety, tolerability, and immunogenicity of RSVpreF. Both the 120-µg dose level and a 60-µg dose level will be evaluated. Up to 120 participants are expected to be enrolled in the Phase 1 cohort and up to 1860 participants will be enrolled in the Phase 2/3 cohort.

- RSVpreF is also being studied in the maternal program, which includes Phase 2b and Phase 3 studies in pregnant women and their infants and a Phase 2b study in nonpregnant women. Details of each of these studies are provided in the RSVpreF IB.

2.3. Benefit/Risk Assessment

- RSV infection is a major cause of severe morbidity among older adults with underlying cardiopulmonary conditions and can cause severe lower respiratory sequelae resulting in hospitalization and respiratory failure.[32] RSV incidence rates among hospitalized patients 85 years of age and older have been found to be similar to children 1 to 2 years of age in Scotland, England, and the Netherlands.[33] Furthermore, adult immunocompromised patients of any age, particularly HSCT and SOT patients as well as persons with underlying heart and lung disease, are at risk for more severe complications of RSV disease, including hospitalizations and ICU admission.[34] Risk factors for progression of RSV disease to viral pneumonia and other complications include an immunocompromised state, underlying heart and lung disease, and living in a long-term care facility.[35] In one study, with a mean age of 53.78 among HSCT and 55 among SOT patients, the mortality from LRTI-RSV was 4.9% and 10.7% for HSCT and SOT recipients, respectively.[6]

- Standard-of-care treatment for RSV in older adults is largely supportive, while targeted therapies have been developed for the pediatric population, including a prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), that binds the RSV F glycoprotein, is recommended for use only in high-risk infants,

and can prevent infant RSV disease.[36] A newer humanized monoclonal antibody targeting the prefusion conformation of RSV F glycoprotein, nirsevimab (Beyfortus, AstraZeneca and Sanofi), was recently approved in the US to prevent LRTI-RSV requiring medical attention and RSV-associated hospitalization in healthy infants and children up to 24 months of age and had been approved for a similar indication in the EU in November 2022.[28,29] Among immunocompromised and nonimmunocompromised adults 18 years of age and older, oral and inhaled ribavirin has been used as an off-label treatment of RSV infection, showing a decrease in mortality in some retrospective cohorts.[37,38]

- With the lack of direct antiviral therapies for the treatment of RSV disease, the limitation of monoclonal antibody prophylaxis for infants and children up to 24 months of age, and the absence of a licensed vaccine to prevent RSV disease in adults under 60 years of age, there exists an unmet medical need for agents that can provide prophylaxis against RSV disease for adults of all ages with high-risk medical conditions for severe RSV disease, including an immunocompromised state.

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RSVpreF		
Pfizer has identified the most common risks for RSVpreF as local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fatigue, headache, diarrhea, joint pain, nausea, vomiting, muscle pain, and fever. Guillain-Barre syndrome has been identified as a potential risk for RSVpreF. Other events of interest include atrial fibrillation, polyneuropathy, preterm birth (delivery at <37 0/7 weeks' gestation), and hypertensive disorders of pregnancy. The identified adverse reactions in local product labels may vary depending on the requirements of the respective regulatory authorities (eg, EU-SmPC and USPI).	These are common adverse reactions seen with other vaccines as well as RSVpreF.[39] Data available from completed and ongoing studies showed a low incidence of severe or serious events, and no clinically concerning safety observations.[30,40] The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, and race/ethnicity. In Study C3671013, conducted in adults 60 years of age and older, there was 1 case of Guillain-Barre syndrome and 1 case of Miller Fisher syndrome (both with a plausible temporal relationship with vaccination). Both cases had confounding factors or alternative etiology. In Study C3671013, conducted in adults 60 years of age and older, there was a nonsignificant numerical imbalance in the number of cases of atrial fibrillation reported for individuals who received RSVpreF compared to individuals who received the placebo. Most of the participants who had atrial fibrillation and received RSVpreF had a preexisting medical history of atrial fibrillation and/or cardiac disease.[41] In Study C3671008, conducted in pregnant individuals, there were no statistically meaningful imbalances between RSVpreF and placebo recipients in the overall rates of preterm birth (5.7% [95% CI: 4.9, 6.5] versus 4.7% [95% CI: 4.1, 5.5],	• The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call and visit, if required, to be conducted per protocol. • All study participants will be observed for at least 30 minutes after vaccination. • AEs and SAEs will be collected throughout the study. • A DMC will review all safety data throughout the study. • Specific references to risks and events of interest are made within the ICD, with reporting instructions if a case is suspected.

	respectively). However, a numerical imbalance was observed in upper-middle-income countries between RSVpreF and placebo recipients. Outcomes in the premature infants were similar between the 2 groups. In Study C3671008, conducted in pregnant individuals, there was a nonsignificant numerical imbalance in hypertensive disorders of pregnancy reported for participants who received RSVpreF compared to participants who received the placebo. The majority of preterm and hypertensive disorders occurred more than 30 days following vaccination.	
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 in Substudy A are detailed in Section 10.7.2.3.

Benefits to individual participants enrolled in Substudy B are detailed in Section 10.8.2.3.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

For Substudy A–specific objectives, endpoints, and estimands, refer to Section 10.7.3.

For Substudy B–specific objectives, endpoints, and estimands, refer to Section 10.8.3.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3 protocol that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults at high risk of severe RSV disease. Each substudy design is detailed separately in the respective substudy appendices. Substudies may be conducted in parallel, as required by the clinical plan, within the framework of this protocol. Table 1 provides an overview of the substudies. For more details on study designs, refer to the appendix of each substudy: Substudy A (Section 10.7.4) and Substudy B (Section 10.8.4).

Table 1. High-Level Overview of Substudies in Protocol

Phase	Group/Age	Study Intervention	Randomization /Blind	Number of Doses to Be Administered During Study	Approximate Number of Participants
Substudy A: Evaluation of RSVpreF in adults ≥18 to <60 years of age at high risk of RSV disease					
3	≥18 Years to <60 years	RSVpreF 120 µg Placebo	2:1 Double-blinded	1	675
Substudy B: Evaluation of RSVpreF in immunocompromised adults ≥18 years of age					
3	≥18 Years to <60 years	RSVpreF 120 µg	Open-label	2	100
	≥60 Years of age				100

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the rationale for the design of the overall study.

See the substudy appendices for the rationales supporting each substudy.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants who align with the population distribution of the country(ies) in which the study is conducted, in the protocol-specified age group, and with the distribution of characteristics, to ensure the study population is representative of the population that will benefit from RSVpreF in clinical practice.

4.3. Justification for Dose

The dose and formulation of RSVpreF selected for use in this study are based on the safety and immunogenicity data from 3 Phase 1/2 studies and the efficacy analyses in the human challenge study and 2 ongoing Phase 3 studies. There were no substantial differences observed between the immunogenicity or reactogenicity of the 120-µg and 240-µg dose levels of the formulation without $Al(OH)_3$. The 120-µg dose, without any adjuvants, has been shown to have low reactogenicity and an acceptable safety profile and will be the dose given in this study.

4.4. End of Study Definition

The end of each substudy is defined as the date of the last visit of the last participant in the substudy. A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit.

The end of the study overall is the last visit of the last participant in the last substudy to be completed.

Each substudy may be analyzed, reported, and disclosed separately.

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:

See Section 10.7.5.1 for Substudy A–specific inclusion criteria.

See Section 10.8.5.1 for Substudy B–specific inclusion criteria.

5.2. Exclusion Criteria

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

See Section 10.7.5.2 for Substudy A–specific exclusion criteria.

See Section 10.8.5.2 for Substudy B–specific exclusion criteria.

5.3. Lifestyle Considerations

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

All pregnancies discovered in female participants and female partners of male participants during study participation, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded in accordance with the EDP (see Section 8.4.5.1) and EDB (see Section 8.4.5.2) reporting processes.

5.4. Screen Failures

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

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

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

See Section 10.7.5.5 for Substudy A–specific temporary delay criteria.

See Section 10.8.5.5 for Substudy B–specific temporary delay criteria.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

For Substudy A, refer to Section 10.7.6.1.

For Substudy B, refer to Section 10.8.6.1.

6.1.1. Administration

Participants will receive study intervention as allocated by the IRT in accordance with the substudy's SoA.

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

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

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

Study intervention administration details will be recorded on the CRF.

See Section 10.7.6.1 for further study intervention administration details for Substudy A.

See Section 10.8.6.1 for further study intervention administration details for Substudy B.

6.1.2. Medical Devices

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

Instructions for medical device use are provided in the IPM.

All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

- 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.

- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

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

- 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.

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

- Study interventions should be stored in their original containers.

- 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.

- Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the preparation and dispensing.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to vaccine groups, and/or the assignment of study intervention to be dispensed to the participant, as applicable to the substudy, will proceed through the use of an IRT system.

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

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

For further details for Substudy A, refer to Section 10.7.6.1.

For further details for Substudy B, refer to Section 10.8.6.1.

6.4. Blinding

Blinding arrangements for participants, site personnel, and the sponsor for Substudy A are detailed in Section 10.7.6.2.

Blinding arrangements for participants, site personnel, and the sponsor for Substudy B are detailed in Section 10.8.6.2. Substudy B is an open-label study.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time as well as the anatomical location of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of the study intervention and study participant identification 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 dosage 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

For Substudy A, refer to Section 10.7.6.7.1.

For Substudy B, refer to Section 10.8.6.7.1.

6.9.2. Permitted Concomitant Vaccinations and Treatments

For Substudy A, refer to Section 10.7.6.7.2.

For Substudy B, refer to Section 10.8.6.7.2.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Substudy A is a single-dose substudy; therefore, this section is not applicable to that substudy.

Substudy B: It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: AEs, participant request, investigator request, and protocol deviation (including no longer meeting all the inclusion criteria or meeting 1 or more exclusion criteria).

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be

evaluated for safety and, where applicable, immunogenicity. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, further study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Select protocol deviations (Note: Receipt of an RSV vaccine outside of the study will result in study withdrawal).

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 receipt of study intervention (Substudy B) and/or 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 further receipt of study intervention or also 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

See Section 10.7.8 for assessments and procedures specific to Substudy A.

See Section 10.8.8 for assessments and procedures specific to Substudy B.

8.1. Administrative and Baseline Procedures

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

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

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

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

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

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

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participations at scheduled visits per the SoA or unscheduled visits.

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

For Substudy A, refer to Section 10.7.8.1.

For Substudy B, refer to Section 10.8.8.1.

8.2.1. RSV Vaccine Antibody Testing

Refer to Section 10.7.8.1.1 for Substudy A details on RSV vaccine antibody testing.

Refer to Section 10.8.8.1.1 for Substudy B details on RSV vaccine antibody testing.

8.2.2. Exploratory Assays, Including Immunogenicity Assessments and Assay Development

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

8.2.3. Biological Samples

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

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.

For blood sampling details, refer to the appendix of each substudy.

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.

For Substudy A, refer to Section 10.7.8.2.

For Substudy B, refer to Section 10.8.8.2.

8.3.1. Physical Examinations

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical

examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.2) must be reported according to the processes in Section 8.4.

8.3.2. Vital Signs

The participant's body temperature will be measured prior to study vaccination as per usual clinical practice. Respiratory rate at baseline will also be assessed.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.2) must be reported according to the processes in Section 8.4.

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, and will be asked to monitor and record local reactions, systemic events, and temperature each evening for 7 days from the day of administration of study intervention (reactogenicity period). 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.

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

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 on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.
- Any local reactions or systemic events occurring within the first 30 minutes after study vaccination must be recorded on the AE page of the CRF.
- If a participant withdraws because of prompted events recorded in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

- If a participant missed reporting any day in the e-diary and reports an event to the study site instead, the event should be recorded on the AE page of the CRF.

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

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

Please note that all provisioned e-diary devices must be collected per the SoA (Section 10.7.1.3 and Section 10.8.1.3).

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.[39]

8.3.4.2. Local Reactions

During the reactogenicity period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary.

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 2. 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 2.

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 or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. A Grade 4 reaction will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.2.3).

If a local reaction persists beyond the end of the e-diary period, the participant will be requested to report that information and/or any new AEs that develop to the investigator.

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

Table 2. Grading Scale for Local Reactions

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

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. Grade 4 local reactions will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

8.3.4.3. Systemic Events

During the reactogenicity e-diary period, participants will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

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 or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. A Grade 4 event will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.2.3).

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

Table 3. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in 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 or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. Grade 4 systemic events will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

8.3.4.4. Temperature

A digital thermometer will be given to the participant with instructions on how to measure temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity reporting period that fever is suspected.

Fever is defined as a temperature of ≥38.0°C (≥100.4°F). 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. Temperatures recorded in degrees Fahrenheit will be

programmatically converted to degrees Celsius and then categorized during analysis as mild, moderate, or severe based on the intensity grading scale provided in Table 4.

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 less than 38.0°C [100.4°F]) in order to collect a stop date in the CRF.

If a fever of >38.9°C (>102.0°F) 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 contact with the participant. Grade 4 fevers will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

Table 4. Ranges for Fever

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fever	≥38.0°C to 38.4°C (100.4-101.1°F)	>38.4°C to 38.9°C (101.2-102.0°F)	>38.9°C to 40.0°C (102.1-104.0°F)	>40.0°C (>104.0°F)

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 contact with the participant. Grade 4 fevers will be collected on the AE CRF and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

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

The definitions of an AE and an SAE can be found in Section 10.2.

The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.5. Device deficiencies are covered in Section 10.5.3.

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 intervention (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 approximately 1 month following the last administration of the study intervention, and AESIs, NDCMCs, and SAEs will be collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected.

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 study intervention, or discontinues from 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 via PSSA or using the Vaccine SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety via PSSA or using the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as

indicated in Section 10.2. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the 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 Section 10.2.

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by 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 EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety 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 the study.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA or using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed 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, congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

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

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

The following events are considered AESIs in Substudy A and Substudy B:

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

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

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4 from the time the participant provides informed consent through the end of study participation. 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.

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.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

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

The definition of a medical device deficiency can be found in Section 10.5.

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

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

Refer to Section 10.5.4 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. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

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

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of 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 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 vaccination error is accompanied by an AE, as determined by the investigator, such vaccination errors occurring to a study participant are recorded on the medication error page of the CRF and, if applicable, any associated serious and nonserious AEs are recorded on the AE page of the CRF.

In the event of a vaccination dosing error, the sponsor should be notified within 24 hours.

Vaccination errors should be reported to Pfizer Safety within 24 hours via PSSA or using a Vaccine SAE Report Form **only when associated with an SAE**.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2 and the appendix of each substudy.

8.9. Health Economics

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

8.10. Unscheduled Reactogenicity Visit

If a severe 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 should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction, systemic event, or fever 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.

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.

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

- Measure temperature.
- Measure the participant's heart rate.

- Measure the participant's blood pressure (seated).
- Measure the minimum and maximum diameters of redness (if present) on the arm in which the study intervention was administered.
- Measure the minimum and maximum diameters of swelling (if present) on the arm in which the study intervention was administered.
- Assess if necrosis is present at the injection site on the arm in which the study intervention was administered.
- Assess if any exfoliative dermatitis is present.
- Assess any injection site pain 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.
- Ask the participant if he/she attended an emergency room visit or was hospitalized.
- For severe pain at the injection site resulting in an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, any necrosis on the arm in which the study intervention was administered, or exfoliative dermatitis, the investigator or qualified designee must assess these events in accordance with the intensity AE grading scale provided in Section 10.2.
- Record AEs, SAEs, and NDCMCs as described in Section 8.4.
- Complete the participant's source documents.
- The investigator or an authorized designee will complete the CRFs.
- The study staff may contact the participant to obtain additional information on events entered into the e-diary, as appropriate.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypothesis

For Substudy A, refer to Section 10.7.9.1.

For Substudy B, refer to Section 10.8.9.1.

9.1.1. Estimands

For Substudy A, refer to Section 10.7.9.1.1.

For Substudy B, refer to Section 10.8.9.1.1.

9.1.2. Multiplicity Adjustment

No multiplicity adjustment will be applied across the substudies.

For Substudy A, refer to Section 10.7.9.1.2.

For Substudy B, refer to Section 10.8.9.1.2.

9.2. Analysis Sets

Refer to the respective appendix for each substudy.

For Substudy A, refer to Section 10.7.9.2.

For Substudy B, refer to Section 10.8.9.2.

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.

Refer to each substudy appendix for a description of the statistical analyses for the substudy endpoints.

For Substudy A, refer to Section 10.7.9.

For Substudy B, refer to Section 10.8.9.

9.3.1. General Considerations

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

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing AE dates will be imputed according to Pfizer safety rules. Completely missing e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially complete e-diary data (ie, 1-6 days of e-diary data are available), it is expected that these missing e-diary days would be queried by the investigator and any missed reported reactogenicity would be entered in the AE CRF; therefore, the primary analysis will use reactogenicity recorded in the AE CRF to impute the partially missed e-diary data to estimate the reactogenicity rates during the 7-day period.

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

9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n), and the denominator (N) used in the percentage calculation. The 95% CI for percentage, and for difference in percentages, may also be presented where appropriate.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[42]

The 95% CI for the difference in proportions will be computed using the Miettinen and Nurminen[43] method. The 95% CI will be presented in terms of percentage.

9.3.1.2. Analyses for Continuous Data

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

9.3.1.2.1. Geometric Means

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

9.3.1.2.2. Geometric Mean Fold Rises

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

distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

9.3.1.2.3. Geometric Mean Ratios

The GMRs will be calculated as the mean of the difference of logarithmically transformed assay results from participants who received RSVpreF in Substudy A to participants ≥60 years of age from Study C3671013 and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.2.4. 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.

9.4. Interim Analyses

Interim analyses will be determined by substudy, and details are provided in each corresponding appendix as necessary.

9.5. Sample Size Determination

Sample size will be determined by substudy, and details are provided in each corresponding appendix.

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.

10.1.3.1. Electronic Consent

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use a DMC. The DMC is independent of the study team and includes a mix of internal and external members. The DMC charter describes the role of the DMC in more detail.

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

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

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

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

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

10.1.9. Use of Medical Records

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

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

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, 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 or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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

10.1.11. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days

upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.12. Sponsor's Medically Qualified Individual

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

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

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

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

10.2.1. Definition of AE

AE Definition

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

Events Meeting 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 via PSSA or on the Vaccine SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety via PSSA or using the Vaccine SAE Report Form and EDP Supplemental Form.
** **EDB** is reported to Pfizer Safety via PSSA or using the Vaccine SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via PSSA or 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:

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 via PSSA or in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare 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, PSSA or eSAE). • 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 the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

10.2.5. Newly Diagnosed Chronic Medical Conditions

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

10.3. Appendix 3: Contraceptive and Barrier Guidance

Not applicable.

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

Potential Cases of Drug-Induced Liver Injury

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

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.5. Appendix 5: 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 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 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/Medical Device Constituent Supplemental Form as outlined in Section 8.4.1.1 and Section 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 product information 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 Section 10.2.

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

Potential participants with chronic stable HIV 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.

10.7. Appendix 7: Substudy A

10.7.1. Substudy A Summary

10.7.1.1. Synopsis

See Section 1.1 for the study synopsis.

10.7.1.2. Schema: Substudy A

Adults ≥18 to <60 years of age at high risk of RSV disease

Adults ≥18 to <60 Years of Age N = 675 Randomized 2:1 RSVpreF : Placebo	Visit 101 (Day 1)	Visit 102 (Month 1) 28 to 35 Days After Vaccination 1	Visit 103 (Month 6) 175 to 189 Days After Vaccination 1
	Vaccination 1	Follow-Up	Follow-Up
RSVpreF / placebo	Blood draw and vaccination 	Blood draw 	

10.7.1.3. Schedule of Activities: Substudy A

Adults ≥18 to <60 years of age at high risk of RSV disease

Visit Number	101	102	103
Visit Description	Vaccination	1-Month Follow-Up	6-Month Safety Follow-Up
Visit Window (Days)	Day 1	28 to 35 Days After Vaccination at Visit 101	175 to 189 Days After Vaccination at Visit 101
Type of Visit	Clinic	Clinic	Telephone or Clinic
Obtain informed consent	X		
Assign single participant number	X		
Obtain demography and significant medical history data	X		
Record current/former tobacco usage	X		

Visit Number	101	102	103
Visit Description	**Vaccination**	**1-Month Follow-Up**	**6-Month Safety Follow-Up**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Vaccination at Visit 101**	**175 to 189 Days After Vaccination at Visit 101**
Type of Visit	**Clinic**	**Clinic**	**Telephone or Clinic**
Perform clinical assessment, including respiratory rate (and physical examination if deemed necessary)	X		
Collect nonstudy vaccine information	X	X	X
Collect prohibited medications and treatments	X	X	X
Confirm inclusion and exclusion criteria	X		
Obtain prevaccination temperature	X		
Review temporary delay criteria	X		
Assign randomization number	X		
Obtain blood sample for antibody assessment	~20 mL	~20 mL	
Administer study intervention	X		
Assess acute reactions for at least 30 minutes after study intervention administration	X		
Dispense measuring device and digital thermometer	X		
Provide e-diary training on daily reactogenicity questionnaire	X		
Assist the participant in downloading the study application onto his or her own device or issue a provisioned device if required for e-diary	X		
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	----------X----------		
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	
Collect the provisioned device or assist the participant with removing the study application from his or her own personal device		X	
Record AEs as appropriate	X	X	
Collect AESIs, SAEs, and NDCMCs as appropriate	X	X	X

10.7.2. Introduction for Substudy A

10.7.2.1. Study Rationale

Substudy A will evaluate the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults considered at high risk of RSV disease due to certain chronic medical conditions.

10.7.2.2. Background

See Section 2.2.

10.7.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy A beyond those detailed in Section 2.3.

Benefits to individual participants enrolled may be:

- Receipt of a potentially efficacious RSV vaccine.
- Contributing to research to help others.

10.7.3. Objectives, Endpoints, and Estimands for Substudy A

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
• To describe the safety profile of RSVpreF as measured by the percentage of participants ≥18 to <60 years of age with high-risk chronic medical conditions reporting local reactions, systemic events, AEs, and SAEs following study intervention administration.	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) • AEs • NDCMCs • SAEs	In participants receiving study intervention: • The proportion of participants reporting local reactions within 7 days following study intervention administration. • The proportion of participants reporting systemic events within 7 days following study intervention administration. • The proportion of participants reporting AEs through 1 month following study intervention administration. • The proportion of participants reporting NDCMCs throughout the study. • The proportion of participants reporting SAEs throughout the study.

Objectives	Endpoints	Estimands
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
• To demonstrate that the immune responses elicited by RSVpreF in adults ≥18 to <60 years of age with high-risk chronic medical conditions are noninferior to the immune responses in vaccinated adults ≥60 years of age in Study C3671013.	RSV A and RSV B serum NTs	In participants who received RSVpreF and in compliance with the key protocol criteria (evaluable immunogenicity population): • GMT ratio (GMR), estimated by the ratio of the GMTs for RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF in Study C3671023 participants to that in Study C3671013 adults ≥60 years of age. • Difference in seroresponse rate of RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF between participants in Study C3671023 and in Study C3671013. Seroresponse is defined as a postvaccination NT ≥4 times the LLOQ if baseline titer is below the LLOQ; or a ≥4-fold rise from baseline if the baseline titer is above the LLOQ.
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
• To describe the immune responses elicited by RSVpreF in adults ≥18 to <60 years of age with high-risk chronic medical conditions.	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 the postvaccination blood sampling visit.

10.7.4. Study Design for Substudy A

10.7.4.1. Overall Design

This is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults considered at high risk of RSV disease due to certain chronic medical conditions.

Approximately 675 participants ≥18 to <60 years of age considered at high risk of RSV disease due to certain chronic medical conditions will be randomized in a ratio of 2:1 to receive either the 120-µg dose level of RSVpreF or placebo. Enrollment will be monitored to help ensure distribution of vaccination across the age range. The duration of study participation for each participant will be approximately 6 months. A reactogenicity e-diary will be used by participants for 7 days from the day of vaccination. The active collection period for AEs will be through approximately 1 month after study intervention administration and for AESIs, SAEs, and NDCMCs through approximately 6 months after study intervention administration. Blood samples will be taken at baseline and 1 month after dose administration for all participants for assessment of immunogenicity.

Adults with high-risk medical conditions who are at significant risk of morbidity and mortality due to RSV infection will be included in this study. High-risk chronic medical conditions are defined in this substudy as:

- Chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus):
  - Duration greater than 6 months.
  - Stable disease not requiring a significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of study intervention.
  - Requires regular medical follow-up, ongoing medication, or hospitalization in the previous year.
- Additional groups at high risk include:
  - Residents of nursing homes and other long-term care facilities.

10.7.4.2. Scientific Rationale for Substudy A Design

See Section 2.1.

Substudy A uses a 1.5-fold noninferiority margin for GMR and a -10% noninferiority margin for seroresponse rates for both RSV A and RSV B, in order to bridge the immune response from the target population to Study C3671013, where efficacy was demonstrated for

RSVpreF in preventing LRTI-RSV. GMRs of RSV NTs at 1 month after vaccination with RSVpreF among participants (≥18 to <60 years of age with high-risk chronic medical conditions) from this study to the participants ≥60 years old from the Study C3671013 immunogenicity subset will be provided along with the associated 2-sided 95% CIs. Study success will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.667 and the lower bound of the 2-sided 95% CI for seroresponse rate differences is greater than -10% for both RSV A and RSV B.

10.7.4.3. Justification for Dose

See Section 4.3.

10.7.4.4. End of Study Definition

See Section 4.4.

10.7.5. Study Population for Substudy A

Participants must meet all of the inclusion criteria and none of the exclusion criteria as specified for Substudy A. Note, a recent systematic literature review collating risk factors for severe RSV disease among adults found more limited data than are available for influenza, which is more widely studied among older adults. However, findings suggest that severe disease risk factors are similar for these 2 respiratory viruses.[25,44] On this basis, comorbidities noted to be risk factors in the influenza vaccine program were used as inclusion criteria for this study.

10.7.5.1. Inclusion Criteria

Participants are eligible to be included in Substudy A only if all of the inclusion criteria apply:

Informed Consent

1. 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.

Age and Sex

2. Participants ≥18 to <60 years of age at study enrollment.

Type of Participant and Disease Characteristics:

3. Life expectancy ≥12 months (365 days) in the opinion of the investigator at enrollment.

4. Participants who are willing and able to comply with all scheduled visits, vaccination plan, lifestyle considerations, and other study procedures.

5. Participants who are considered at high risk of RSV disease by virtue of the following:

    - Adults with chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus).

      Chronic medical conditions for this substudy are defined as:

        - Duration greater than 6 months.
        - Stable disease not requiring a significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of study intervention.
        - Requires regular medical follow-up or ongoing medication or hospitalization in the previous year.

    - Additional groups at high risk include:

        - Residents of nursing homes and other long-term care facilities.

10.7.5.2. Exclusion Criteria

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

Medical Conditions:

1. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s) or any related vaccine.
3. Participants who do not have adequate deltoid muscle mass to allow intramuscular vaccination, in the opinion of the investigator.
4. 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.
5. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

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

   Note: Specific criteria for participants with known stable infection with HIV can be found in Section 10.6, Appendix 6.

Prior/Concomitant Therapy:

7. Individuals who receive chronic systemic treatment with immunosuppressive therapy, including cytotoxic agents, immunosuppressive monoclonal antibodies, systemic corticosteroids*, eg, for cancer or an autoimmune disease, or radiotherapy, from 60 days before study intervention administration or planned receipt throughout the study.

   *Applies to systemic corticosteroids administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent (eg, for cancer or an autoimmune disease). Systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

8. Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration or planned receipt of these medications prior to the final 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 7.

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

Prior/Concurrent Clinical Study Experience:

10. Participation in other studies involving an investigational product within 28 days prior to consent and/or through and including the 6-month follow-up visit.

    Note: This criterion does not apply to participants who are participating in a follow-up period for another study involving a study intervention that is an investigational drug or vaccine, if receipt of the last dose was at least 6 months prior to consenting for this study and there is no further dosing anticipated from the previous study during the participant's participation in this study.

Other Exclusion Criteria:

11. 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.

10.7.5.3. Lifestyle Considerations

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

All pregnancies discovered in female participants and female partners of male participants, during study participation, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded in accordance with the EDP (see Section 8.4.5.1) and EDB (see Section 8.4.5.2) reporting processes.

10.7.5.4. Screen Failures

See Section 5.4.

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

The following conditions may allow a participant to be randomized once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 101 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

- Current febrile illness (temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration.
- Receipt of any live vaccine within 28 days before study intervention administration. Receipt of any nonlive vaccine (including COVID-19 vaccines authorized for temporary or emergency use) within 14 days before study intervention administration.
- Anticipated receipt of any nonstudy vaccine within 14 days after study intervention administration.
- 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.

10.7.6. Study Intervention and Concomitant Therapy for Substudy A

For the purposes of this study, study intervention refers to:

- RSVpreF.
- Placebo (lyophile match).

10.7.6.1. Study Intervention(s) Administered for Substudy A

Study Intervention(s)		
Intervention name	RSVpreF	Placebo
Type	Vaccine	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose formulation	The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The RSV drug product will be 120 µg of the RSV prefusion F antigen. The drug product is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The drug product will be reconstituted by a diluent consisting of sterile water in a PFS. The lyophilized drug product contains excipients that, after reconstitution, will yield a solution as detailed in the IB. The fill volume of the drug product vial and diluent PFS are designed such that the 120-µg vaccine dose is delivered by injecting the entire contents of the syringe.	Placebo will be a lyophile match to the vaccine, which will consist of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients. The placebo is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The lyophilized white cake will be reconstituted by a diluent consisting of sterile water in a PFS. The physical appearance of the reconstituted RSVpreF and placebo will be matched, and **Substudy A** will be conducted in a double-blinded manner. The fill volume of the placebo vial and diluent PFS is designed such that the intended placebo dose is delivered by injecting the entire contents of the syringe to match the 120-µg vaccine dose.
Unit dose strength(s)	120 µg	N/A
Route of administration	Intramuscular	Intramuscular
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Study intervention will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.	Study intervention will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements
SRSD	IB	IB

Study Arms – Substudy A		
Arm Title	RSVpreF	Placebo
Arm Description	Participants will receive RSVpreF 120 µg at Visit 101	Participants will receive placebo at Visit 101

10.7.6.1.1. Administration

Participants will receive 1 dose of study intervention in accordance with the substudy's SoA Section 10.7.1.3. For other details regarding study intervention administration, see Section 6.1.1. The study intervention will be administered into the deltoid muscle, preferably of the nondominant arm unless medically contraindicated in which case the injection may be administered in the dominant arm, by appropriately designated study staff at the investigator site.

10.7.6.1.2. Medical Devices

See Section 6.1.2.

10.7.6.1.3. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.7.6.1.4. Assignment to Study Intervention

See Section 6.3.

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

Study intervention will be dispensed as summarized in the SoA for Substudy A.

10.7.6.2. Blinding for Substudy A

10.7.6.2.1. Blinding of Participants

Substudy A is a double-blinded study. Participants will be blinded to their assigned study intervention.

10.7.6.2.2. Blinding of Site Personnel

Substudy A is double-blinded, as the physical appearance of RSVpreF and placebo will be matched. Investigators and other site staff will be blinded to participants' assigned study intervention.

10.7.6.2.3. Blinding of the Sponsor

The majority of sponsor staff will be blinded to participants' assigned study intervention. All laboratory testing personnel performing serological assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff will be unblinded (further details will be provided in the DMC charter and other study documents): An unblinded vendor supporting interactions with the DMC. This will comprise a statistician and a programmer(s). The unblinded safety analysis for the DMC will be performed by Pfizer/vendor programmers who are separate from the study. Sponsor staff involved in the assignment or distribution of study intervention are also unblinded.

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

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

10.7.6.3. Study Intervention Compliance

See Section 6.5.

10.7.6.4. Dose Modification

Not applicable.

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

See Section 6.7.

10.7.6.6. Treatment of Overdose

See Section 6.8.

10.7.6.7. Prior and Concomitant Therapy for Substudy A

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

- Any vaccinations received from 28 days prior to study enrollment until the last study visit.
- Prohibited medications and treatments listed in Section 10.7.6.7.1 (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.

10.7.6.7.1. Prohibited Concomitant Vaccinations and Treatments for Substudy A

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 should not be withheld if required for a participant's medical care.

- Receipt of any nonstudy RSV vaccine at any time prior to or during study participation.
- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.

  Note: COVID-19 vaccines authorized for temporary or emergency use will not be prohibited during the course of this study if administered more than 14 days prior to study intervention administration or at least 14 days after study intervention administration.
- Receipt of blood/plasma products or immunoglobulin (IVIG, SCIG) prior to the final 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 7.
- Nonstudy vaccines may not be given concomitantly with the study intervention or within 14 days after study intervention administration, except if medically necessary (eg, during an outbreak or pandemic situation).
- Receipt of chronic systemic treatment with known immunosuppressant medications within 60 days before study intervention administration through conclusion of the study.

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

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

- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted before administration of study intervention.

  Note: 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.

10.7.6.7.2. Permitted Concomitant Vaccinations and Treatments for Substudy A

- Medication other than that described as prohibited in Section 10.7.6.7.1 required for treatment of preexisting conditions, acute illness, or to treat symptoms associated with study intervention administration is permitted.

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

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

10.7.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal for Substudy A

Substudy A is a single-dose study; therefore, discontinuation of study intervention is not applicable.

See Section 7.2 for information regarding participant discontinuation/withdrawal from the study.

10.7.8. Study Assessments and Procedures for Substudy A

Refer to Section 8 and the following subsections:

- Section 8.1 Administrative and Baseline Procedures
- Section 8.1.1 Telehealth Visits

10.7.8.1. Immunogenicity Assessments

10.7.8.1.1. RSV Vaccine Antibody Testing

Refer to Section 8.2.3 for general information regarding use and storage of biological samples.

Blood samples (approximately 20 mL per sample) will be collected from participants for immunogenicity testing as specified in the Substudy A SoA (refer to Section 10.7.1.3). The total blood sampling volume for individual participants in Substudy A is approximately 40 mL.

RSV A– and RSV B–neutralizing antibody titers will be measured for each blood sample at each time point, and reported as the NTs. Sera collected will be tested concurrently with sera collected before vaccination and 1 month after vaccination with RSVpreF from the Study C3671013 immunogenicity subset (participants ≥60 years old) so that immunobridging can be assessed.

Blood 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.

10.7.8.2. 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.

Refer to Section 8.3 and the following subsections:

- Section 8.3.1 Physical Examinations
- Section 8.3.2 Vital Signs
- Section 8.3.3 Clinical Safety Laboratory Assessments
- Section 8.3.4 Electronic Diary for Reactogenicity

E-diary assessments are included in Substudy A for participants' reporting of local reactions and systemic events for 7 days from the day of each administration of the study intervention.

Participants will receive reminders to complete the vaccination e-diary on a daily basis, starting on the day of vaccination (Day 1) through Day 7 after each vaccination. Refer to Section 8.3.4 for details.

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

Refer to Section 8.4 and the following subsections:

- Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information
- Section 8.4.2 Method of Detecting AEs and SAEs
- Section 8.4.3 Follow-Up of AEs and SAEs
- Section 8.4.4 Regulatory Reporting Requirements for SAEs
- Section 8.4.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
- Section 8.4.6 Cardiovascular and Death Events
- Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs
- Section 8.4.8 Adverse Events of Special Interest
- Section 8.4.9 Medical Device Deficiencies
- Section 8.4.10 Vaccination Errors

10.7.8.4. Substudy A Procedures

10.7.8.4.1. Visit 101 – Vaccination (Clinic, Day 1)

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

The investigator or his or her 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 study intervention administration** 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 full date of birth will be collected to critically evaluate the immune response, and safety profile by age.
- Obtain and record any medical history of clinical significance, including:
  - Heart disease;
  - Lung disease;
  - Asthma;
  - Diabetes mellitus/metabolic disease;
  - Liver disease;
  - Renal disease;
  - Neurologic disease;
  - Hematologic disease;
  - Resident of nursing home/long-term care facility.
  - In addition, for specific criteria for participants with known stable infection with HIV, please refer to Section 10.6, Appendix 6.
- Obtain and record current/former tobacco usage.
- Perform a clinical assessment, including baseline respiratory rate. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Obtain details of any nonstudy vaccinations, prohibited medications and treatments as described in Section 10.7.6.7.
- **Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.**

- Measure and record prevaccination temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 10.7.5.5.
- 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.
- Qualified site staff member(s) will administer a single dose of study intervention into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IPM for further 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 AE page of the CRF, and on an SAE form as applicable.
- Explain the e-diary technologies available for this study (see Section 8.3.4) and assist the participant in downloading the study application onto his or her 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, with Day 1 being the day of vaccination.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Ask the participant to contact the site staff or investigator immediately if he/she 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 (as detailed in Section 8.10):
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring >20 measuring device units (greater than 10 cm).
  - Severe pain at the injection site.
  - Any severe systemic event.

- Remind the participant that study staff may contact him or her to obtain additional information on events entered into the e-diary.
- Remind participants to inform the study staff of any AEs, AESIs, SAEs, and NDCMCs that occur for the duration of the trial as described in Section 8.4.
- Remind the participant to bring the e-diary to the next 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.

10.7.8.4.2. Visit 102 – 1-Month Follow-Up (Clinic, 28 to 35 Days After Vaccination at Visit 101)

- Obtain details of any nonstudy vaccinations, and prohibited medications and treatments as described in Section 10.7.6.7.
- Collect a blood sample of approximately 20 mL.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF. Any ongoing reactions must be assessed at the next contact.
- Collect the provisioned device or assist the participant with removing the study application from his or her own personal device.
- Record AEs, AESIs, SAEs, and NDCMCs as described in Section 8.4.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.7.8.4.3. Visit 103 – 6-Month Safety Follow-Up (Telephone or Clinic, Within 175 to 189 Days After Vaccination at Visit 101)

- Contact the participant by telephone. This visit can be conducted as a clinic visit if the investigator deems it is necessary for the participant to be seen in person.
- Obtain details of any nonstudy vaccinations, and prohibited medications and treatments as described in Section 10.7.6.7.1.

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

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

See Section 8.10.

10.7.9. Statistical Considerations for Substudy A

See Section 9 for general protocol statistical considerations and see specific substudy statistical considerations below.

10.7.9.1. Statistical Hypotheses

For the primary immunogenicity objective, there are a total of 4 tests (2 for RSV A and 2 for RSV B). The primary immunogenicity objective will be evaluated by the following null hypothesis:

- H_0: $\ln(\mu_1) - \ln(\mu_2) \leq -\ln(1.5)$ or $p_1 - p_2 \leq -10\%$ vs
- H_a: $\ln(\mu_1) - \ln(\mu_2) > -\ln(1.5)$ and $p_1 - p_2 > -10\%$

where $-\ln(1.5)$ corresponds to a 1.5-fold margin for noninferiority in GMR, $\ln(\mu_1)$ is the mean of the natural logarithm-transformed serum NT at 1 month after vaccination from participants who received the same dose level of RSVpreF in this study (participants ≥18 to <60 years of age with high-risk chronic medical conditions), and $\ln(\mu_2)$ is the mean of the natural logarithm-transformed serum NT from participants who received RSVpreF in the C3671013 study immunogenicity subset (participants ≥60 years of age); -10% is a noninferiority margin for seroresponse rate, p_1 is the seroresponse rate at 1 month after vaccination from participants ≥18 to <60 years of age who received RSVpreF and have high-risk chronic medical conditions, and p_2 is the seroresponse rate at 1 month after vaccination from participants who received RSVpreF in the C3671013 study immunogenicity subset (participants ≥60 years of age).

Seroresponse is defined as a postvaccination antibody titer ≥4 times the LLOQ for a baseline titer below the LLOQ (seronegative); or a ≥4-fold rise from baseline to after vaccination if the baseline titer is above the LLOQ (seropositive).

Noninferiority will be declared if both the null hypothesis of GMR and the null hypothesis of difference in seroresponse rates are rejected for both RSV A and RSV B serum NTs, with a type I error (2-sided) of 5%.

10.7.9.1.1. Estimands

The estimands corresponding to each primary, secondary, and exploratory objective (if any) are described in Section 10.7.3.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (Section 10.7.9.2). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing immunogenicity results will not be imputed, as MCAR is assumed.

10.7.9.1.2. Multiplicity Adjustment

No multiplicity adjustment will be applied for this study because all 4 (2 endpoints for 2 RSV subgroups) statistical hypotheses must be rejected to declare noninferiority. Each of the 4 statistical tests will use a 2-sided alpha level of 0.05.

10.7.9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined for this substudy:

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

Defined Analysis Set	Description
Evaluable immunogenicity population	This population will be defined for Substudy A, and it includes all participants who meet the following criteria: • Are eligible for Substudy A; • Receive the study interventions to which they were randomized; • Have the 1-month postvaccination blood collection within an appropriate window; • Have at least 1 valid and determinate assay result 1 month after vaccination; • Have no major protocol violations from vaccination through the 1-month postvaccination blood draw.

Defined Analysis Set	Description
mITT immunogenicity population	All participants who were randomized and had at least 1 valid and determinate assay result after receiving study intervention in this substudy.

10.7.9.3. Statistical Analysis

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.

10.7.9.3.1. General Considerations

Refer to Section 9.3.1 for general considerations of the statistical analyses.

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

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

Table 5. Primary Endpoint Analyses

Endpoint	Statistical Analysis Methods
Safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each 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 and SAEs will be categorized according to MedDRA terms. All of AEs through 1 month following study intervention administration and all AESIs, SAEs, and NDCMCs 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

Table 5. Primary Endpoint Analyses

Endpoint	Statistical Analysis Methods
	described in detail in the SAP. (2) Tier 2 events are considered "relatively common" events; a MedDRA PT is defined as a Tier 2 event if there are at least 1% of participants in any vaccine group reporting the event, in any age stratum. (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. • 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 asymptotic p-values will be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.
Immunogenicity	• RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF among participants who received RSVpreF from Substudy A to the participants ≥60 years from the Study C3671013 immunogenicity subset will be compared with a linear regression model that includes groups (current study vs C3671013), corresponding baseline titers, and sex. The model-adjusted GMR comparing groups (18 to <60 years of age with high risk in C3671023 Substudy A vs 60 years and older in C3671013) and corresponding 95% CI will be provided. • Difference in seroresponse rate of RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF among participants who received RSVpreF from Substudy A to the participants ≥60 years from the Study C3671013 immunogenicity subset will be provided along with the associated 2-sided 95% CIs. • Using a 1.5-fold noninferiority margin and a noninferiority margin of -10%, study success will be declared if the lower bound of the 2-sided 95% CI of model-adjusted GMR is greater than 0.667, and the lower bound of the 2-sided 95% CI of the seroresponse rate difference is greater than -10% for both RSV A and RSV B subgroups. • Empirical RCDCs will be provided for RSV A and RSV B serum NTs at 1 month after vaccination (Section 9.3.1.2.4).

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

Table 6. Secondary Endpoint Analyses

Endpoint	Statistical Analysis Methods
Immunogenicity	• GMTs and their associated 95% CIs will be descriptively summarized, by vaccine group, for both RSV A and RSV B serum NT subgroups at each blood sampling visit (Section 9.3.1.2.1). • GMFRs 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 NT subgroups NTs (Section 9.3.1.2.2).

10.7.9.4. Interim Analysis

No interim analysis is planned.

10.7.9.4.1. Analysis Timing

When all primary safety endpoints and primary immunogenicity endpoint data become available, Substudy A will be unblinded for the primary analysis. All safety data collected throughout the study will be cleaned, and primary and secondary immunogenicity data through 1 month after vaccination will also be cleaned and included in the analysis, with all type I error spent in this primary analysis.

10.7.9.5. Sample Size Determination

The sample size of Substudy A is based on demonstrating noninferiority with respect to RSV A and RSV B serum NTs from participants who received RSVpreF compared to serum blood samples taken from RSVpreF-vaccinated older adults from the C3671013 study, using a 1.5-fold noninferiority margin for GMR and a -10% noninferiority margin for difference in seroresponse rate for both RSV A and RSV B. A total of 4 comparisons will be made.

Power is calculated using PROC POWER in SAS Version 9.4. For each comparison, the probability of meeting the noninferiority criterion based on the 95% CI is calculated. The resulting 4 probabilities are then multiplied to estimate the power for declaring overall noninferiority of the vaccine (noninferiority demonstrated for both RSV A and RSV B).

The natural log of NTs is assumed to follow a normal distribution. The ratio of GMTs for participants who received RSVpreF in Substudy A to the GMTs for matched participants who received RSVpreF in Study C3671013 (participants ≥60 years of age) is assumed to be 1 for both RSV A and RSV B (ie, assumed GMR = 1). Common assay SD (in natural logarithm scale) is assumed to be 1.1 for both RSV A and RSV B.

The power calculation for difference in seroresponse rate is based on an unconditional exact test. The difference in seroresponse rate for participants who received RSVpreF in Substudy A to the seroresponse rate for matched participants who received RSVpreF in Study C3671013 (participants ≥60 years of age) is assumed to be 0 for both RSV A and RSV B. The common seroresponse rate is assumed to be 0.82 for both RSV A and RSV B. With equal sample sizes in the 2 groups (Substudy A participants vs RSVpreF recipients ≥60 years of age from Study C3671013), 400 evaluable participants per age group will provide an overall power of 91.2% to demonstrate that the immune response from Substudy A is noninferior to the immune response from RSVpreF recipients ≥60 years of age from Study C3671013, which has demonstrated efficacy, using a 1.5-fold noninferiority margin for GMR and a -10% noninferiority margin for difference in seroresponse rate. As the comparison will use serology data from Study C3671013, 400 participants from the Study C3671013 immunogenicity subset who received RSVpreF and met the evaluable immunogenicity definition (assuming that all will have determinate NT results) will be randomly selected, and their sera will be tested for NTs at the same time with all sera collected from the RSVpreF recipients in Substudy A. With a 2:1 randomization, assuming a ~10% nonevaluable rate, approximately 675 participants are expected to be enrolled in this study. Refer to Table 7 for more information.

Table 7. Power to Show Noninferiority of RSV A and RSV B Serum Neutralizing Titers in Substudy A in Study C3671023 Compared to Adults ≥60 Years of Age in Study C3671013

Endpoint	Antigen/ Strain for Comparison	Common SD (Natural Log)/Response Rate[a]	Assumed Difference	NI Margin[b]	N Evaluable RSVpreF Recipients/Group		Power[c]
					Adults ≥18 to <60 Years of Age (Study C3671023 Substudy A)	Adults ≥60 Years of Age (Study C3671013)	
RSV GMR	Subgroup A	1.1	GMR=1	1.5-Fold	400	400	>99.9%
	Subgroup B	1.1	GMR=1	1.5-Fold	400	400	>99.9%
RSV difference in seroresponse rate	Subgroup A	82%	0	-10%	400	400	95.5%
	Subgroup B	82%	0	-10%	400	400	95.5%
Power to show NI for both RSV A and RSV B							**91.2%**

a. Reference Study C3671013.
b. The NI is met if the lower limit of the 95% CI for the GMT ratio ([≥18-year-olds to <60-year-olds in Study C3671023] / [≥60-year-olds in Study C3671013]) is >0.667, and if the lower limit of the 95% CI for the difference in seroresponse rate ([≥18-year-olds to <60-year-olds in Study C3671023] / [≥60-year-olds in Study C3671013]) is >-10%.
c. At the 0.05 alpha level (2-sided).

10.8. Appendix 8: Substudy B

10.8.1. Substudy B Summary

10.8.1.1. Synopsis

See Section 1.1 for the study synopsis.

10.8.1.2. Schema: Substudy B

Immunocompromised adults ≥18 years of age

Immunocompromised Adults ≥18 Years of Age N = 200 Open-Label RSVpreF	Visit 201 (Day 1)	Visit 202 (Month 1) 28 to 35 Days After Vaccination 1	Visit 203 (Month 2) 28 to 35 Days After Vaccination 2	Visit 204 (Month 7) 175 to 189 Days After Vaccination 2
	Vaccination 1	Vaccination 2	Follow-Up	Follow-Up
RSVpreF	Blood draw and vaccination 	Blood draw and vaccination 	Blood draw 	

10.8.1.3. Schedule of Activities: Substudy B

Immunocompromised adults ≥18 years of age

Visit Number	201	202	203	204
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-Up	6-Month Safety Follow-Up
Visit Window (Days)	Day 1	28 to 35 Days After Vaccination 1	28 to 35 Days After Vaccination 2	175 to 189 Days After Vaccination 2
Type of Visit	Clinic	Clinic	Clinic	Telephone or Clinic
Obtain informed consent	X			
Assign single participant number	X			
Obtain demography and significant medical history data	X			
Record current/former tobacco usage	X			
Perform clinical assessment, including respiratory rate (and physical examination if deemed necessary)	X			

Visit Number	201	202	203	204
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-Up	6-Month Safety Follow-Up
Visit Window (Days)	Day 1	28 to 35 Days After Vaccination 1	28 to 35 Days After Vaccination 2	175 to 189 Days After Vaccination 2
Type of Visit	Clinic	Clinic	Clinic	Telephone or Clinic
Collect nonstudy vaccine information	X	X	X	X
Collect prohibited medication	X	X	X	X
Collect concomitant therapy, oral corticosteroids, chemotherapy, immunotherapy, immunomodulator/ biologic treatments, and immunosuppressive treatment	X	X	X	X
Confirm inclusion and exclusion criteria	X	X		
Obtain prevaccination temperature	X	X		
Review temporary delay criteria	X	X		
Obtain the participant's study intervention kit number using the IRT system	X	X		
Obtain blood sample for antibody assessment	~20 mL	~20 mL	~20 mL	
Administer study intervention	X	X		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X		
Dispense measuring device and digital thermometer	X			
Provide e-diary training on daily reactogenicity questionnaire	X	X		
Assist the participant in downloading the study application onto his or her own device or issue a provisioned device if required for e-diary	X			
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	----------X----------			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X	
Collect the provisioned device or assist the participant with removing the study application from his or her own personal device			X	
Record AEs as appropriate	X	X	X	
Collect AESIs, SAEs, and NDCMCs as appropriate	X	X	X	X

10.8.2. Introduction for Substudy B

10.8.2.1. Study Rationale

Substudy B will evaluate the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in immunocompromised adults ≥18 years of age.

10.8.2.2. Background

See Section 2.2.

10.8.2.3. Benefit/Risk Assessment

No additional risks are identified for Substudy B beyond those detailed in Section 2.3.

Benefits to individual participants enrolled may be:

- Receipt of a potentially efficacious RSV vaccine.
- Contributing to research to help others.

10.8.3. Objectives, Endpoints, and Estimands for Substudy B

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
• To describe the safety profile of RSVpreF as measured by the percentage of immunocompromised participants ≥18 years of age reporting local reactions, systemic events, AEs, and SAEs following study intervention administration.	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) • AEs • NDCMCs • SAEs	In participants receiving study intervention: • The proportion of participants reporting local reactions within 7 days following each study intervention administration. • The proportion of participants reporting systemic events within 7 days following each study intervention administration. • The proportion of participants reporting AEs through 1 month following the last dose of study intervention administration. • The proportion of participants reporting NDCMCs throughout the study. • The proportion of participants reporting SAEs throughout the study.

Objectives	Endpoints	Estimands
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
• To describe the immune responses elicited by RSVpreF in immunocompromised adults ≥18 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 each postvaccination blood sampling visit.

10.8.4. Study Design for Substudy B

10.8.4.1. Overall Design

This is a Phase 3, open-label, multicenter study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in immunocompromised adults.

Approximately 200 immunocompromised adults ≥18 years of age will receive an open-label 120-µg dose of RSVpreF at Visit 201 and Visit 202 with an interval of 1 month (2 doses). Within Substudy B, approximately 100 participants will be ≥60 years of age and approximately 100 participants will be ≥18 to <60 years of age. Enrollment will be monitored to help ensure distribution of vaccination across the age range and underlying immunocompromising conditions. The duration of study participation for each participant will be approximately 7 months. A reactogenicity e-diary will be used by participants for 7 days from the day of each vaccination. The active collection period for AEs will be through approximately 1 month after the last vaccination and for AESIs, SAEs, and NDCMCs through approximately 6 months after the last vaccination. Blood samples will be taken at baseline and 1 month after each vaccination for all participants for assessment of immunogenicity.

10.8.4.2. Scientific Rationale for Substudy B Design

See Section 2.1 and Section 10.8.4.3.

10.8.4.3. Justification for Dose

The final dose and formulation of RSVpreF selected for use in this study are based on the safety and immunogenicity data from 3 Phase 1/2 studies, the efficacy analyses in the human challenge study, and 2 ongoing Phase 3 studies. There were no substantial differences observed between the immunogenicity or reactogenicity of the 120-µg and 240-µg dose levels of the formulation without $Al(OH)_3$. The 120-µg dose, without any adjuvants, has

been shown to have low reactogenicity and an acceptable safety profile and will be the dose given in this study.

Immunocompromised hosts have been found to have reduced responses to various vaccines, eg, pneumococcal conjugate and mRNA SARS-CoV-2 vaccines.[45,46,47]

To date, no data exist regarding RSVpreF immunogenicity in the immunocompromised population. However, given the data showing diminished responses to other vaccines, it is reasonable to assess immunogenicity after a second dose of RSVpreF.

These data and the need to achieve protection before RSV season supports the strategy of administering a second dose 1 month after initial vaccination.

10.8.4.4. End of Study Definition

See Section 4.4.

10.8.5. Study Population for Substudy B

Participants must meet all of the inclusion criteria and none of the exclusion criteria as specified for Substudy B.

10.8.5.1. Inclusion Criteria

Participants are eligible to be included in Substudy B only if all of the inclusion criteria apply:

Informed Consent

1. 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.

Age and Sex

2. Participants ≥18 years of age at study enrollment.

Type of Participant and Disease Characteristics:

3. Life expectancy ≥12 months (365 days) in the opinion of the investigator at enrollment.

4. Participants who are willing and able to comply with all scheduled visits, vaccination plan, lifestyle considerations, and other study procedures.

5. Participants who are immunocompromised by virtue of the following:

    - Having known advanced NSCLC with at least 1 of the following:

- Has received initial or maintenance chemotherapy at least 2 weeks (14 days) before enrollment (or is treatment-naïve), and is not expected to receive chemotherapy within at least 2 weeks (14 days) after dose administration of initial vaccination or second vaccination; and/or

- Is receiving checkpoint inhibitor treatment (PD-1/PD-L1 inhibitor, CTLA-4 inhibitor) and has undergone at least 1 treatment cycle prior to enrollment; or

- Is receiving targeted drug therapy (EGFR, ALK, ROS1, BRAF, RET, MET, NTRK inhibitors) and has undergone at least 1 treatment cycle prior to enrollment.

OR

- Is currently undergoing maintenance hemodialysis treatment secondary to end-stage renal disease.

OR

- Is on active immunomodulator therapy (eg, TNFα inhibitor, tofacitinib, or MTX) for an autoimmune inflammatory disorder (eg, inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, or inflammatory bowel disease, such as ulcerative colitis or Crohn's disease) at a stable* dose.

  *Stable dose is defined as receiving the same dose for at least 3 months (84 days) with no changes in the 28 days prior to enrollment. See also Section 10.8.6.7.2 for details on stable dose for MTX.

OR

- Is receiving an SOT (kidney, liver, lung, or heart) at least 3 months (84 days) prior to enrollment (Visit 201) and with no acute rejection episodes within 2 months (60 days) prior to enrollment (Visit 201).

10.8.5.2. Exclusion Criteria

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

Medical Conditions:

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

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

3. Participants with a history of transplant rejection, or PTLD, or participants who have had treatment for these conditions within 3 months (84 days) prior to study enrollment.

4. Participants who do not have adequate deltoid muscle mass to allow intramuscular vaccination, in the opinion of the investigator.

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

   Note: Specific criteria for participants with known stable infection with HIV can be found in Section 10.6, Appendix 6.

Prior/Concomitant Therapy:

6. Receipt of investigational or approved monoclonal antibodies against RSV within 6 months before study intervention administration.

7. Receipt of blood/plasma products or immunoglobulin (IVIG, SCIG) within 60 days before study intervention administration or planned receipt of these medications prior to the final blood draw.

   Note: Please see the inclusion criteria in Section 10.8.5.1 regarding criteria for targeted immunoglobulin therapies for underlying medical conditions.

   Note: Monoclonal antibodies with targeted mechanisms of action used in the management of chronic illnesses (eg, migraine headaches, osteoporosis) are permitted.

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

Prior/Concurrent Clinical Study Experience:

9. Participation in other studies involving an investigational product within 28 days prior to consent and/or through and including the 6-month follow-up visit.

   Note: This criterion does not apply to participants who are participating in a follow-up period for another study involving a study intervention that is an investigational drug or vaccine, if receipt of the last dose was at least 6 months prior to consenting for this study and there is no further dosing anticipated from the previous study during the participant's participation in this study.

Other Exclusion Criteria:

10. 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.

10.8.5.3. Lifestyle Considerations

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

All pregnancies discovered in female participants and female partners of male participants during study participation, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded in accordance with the EDP (see Section 8.4.5.1) and EDB (see Section 8.4.5.2) reporting processes.

10.8.5.4. Screen Failures

See Section 5.4.

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

The following conditions may allow a participant to be vaccinated once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 201 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

- Current febrile illness (temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration.
- Receipt of any live vaccine within 28 days before study intervention administration. Receipt of any nonlive vaccine (including COVID-19 vaccines authorized for temporary or emergency use) within 14 days before study intervention administration.
- Anticipated receipt of any nonstudy vaccine within 14 days after study intervention administration.

10.8.6. Study Intervention and Concomitant Therapy for Substudy B

For the purposes of this study, study intervention refers to:

- RSVpreF.

10.8.6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention name	RSVpreF
Type	Vaccine
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose formulation	The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The RSV drug product will be 120 µg of the RSV prefusion F antigen. The drug product is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The drug product will be reconstituted by a diluent consisting of sterile water in a PFS. The lyophilized drug product contains excipients that, after reconstitution, will yield a solution as detailed in the IB. The fill volume of the drug product vial and diluent PFS are designed such that the 120-µg vaccine dose is delivered by injecting the entire contents of the syringe.
Unit dose strength(s)	120 µg
Route of administration	Intramuscular
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and labeling	Study intervention will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.
SRSD	IB

Study Arms – Substudy B	
Arm Title	RSVpreF
Arm Description	Participants will receive RSVpreF 120 µg at Visits 201 and 202

10.8.6.1.1. Administration

Participants will receive 2 doses of study intervention in accordance with the substudy's SoA. For other details regarding study intervention administration, see Section 6.1.1. The study intervention will be administered into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

10.8.6.1.2. Medical Devices

See Section 6.1.2.

10.8.6.1.3. Preparation, Handling, Storage, and Accountability

See Section 6.2.

10.8.6.1.4. Assignment to Study Intervention

See Section 6.3.

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

Study intervention will be dispensed at the study visits as summarized in the SoA for Substudy B.

10.8.6.2. Blinding for Substudy B

Substudy B is an open-label study.

10.8.6.2.1. Blinding of Participants

Participants will not be blinded to their assigned study intervention.

10.8.6.2.2. Blinding of Site Personnel

Investigators and other site staff will not be blinded to participants' assigned study intervention.

10.8.6.2.3. Blinding of the Sponsor

Pfizer staff will be unblinded to participants' assigned study intervention.

10.8.6.2.4. Breaking the Blind

Not applicable. Substudy B is an open-label study.

10.8.6.3. Study Intervention Compliance

See Section 6.5.

10.8.6.4. Dose Modification

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

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

See Section 6.7.

10.8.6.6. Treatment of Overdose

See Section 6.8.

10.8.6.7. Prior and Concomitant Therapy for Substudy B

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

- Any vaccinations received from 28 days prior to study enrollment until the last study visit.
- Baseline and concomitant therapy, oral corticosteroids, chemotherapy, immunotherapy, immunomodulator/biologic treatments, and immunosuppressive regimens. These will be recorded and include the name of the medication, start date, dose, unit, route, and frequency.
- Prohibited medications and treatments listed in Section 10.8.6.7.1 (with the exception of antipyretics and other pain medications to prevent symptoms), if taken, will be recorded and include the start and stop dates, name of the medication, dose, unit, route, and frequency.

10.8.6.7.1. 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 should not be withheld if required for a participant's medical care.

- Receipt of any nonstudy RSV vaccine at any time prior to or during study participation.
- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.

  Note: COVID-19 vaccines authorized for temporary or emergency use will not be prohibited during the course of this study if administered more than 14 days prior to study intervention administration or at least 14 days after study intervention administration.
- Receipt of blood/plasma products or immunoglobulin (IVIG, SCIG) prior to the final blood draw.

Note: Monoclonal antibodies with targeted mechanisms of action used in the management of chronic illnesses (eg, migraine headaches, osteoporosis) are permitted.

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

- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted before administration of study intervention.

  Note: 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.

10.8.6.7.2. Permitted Concomitant Vaccinations and Treatments

- Oral corticosteroids, stable MTX, and NSAIDs are permitted.

- For participants receiving MTX therapy, stable is defined as receiving MTX for at least 3 months (84 days) prior to Day 1, with no dose changes in the 28 days prior to Day 1, and not exceeding a dose of 25 mg/week.

- For participants not receiving MTX therapy, treatment with MTX must have been stopped at least 3 months (84 days) prior to Day 1 and not be expected to be initiated prior to Dose 2.

- Immunosuppressant/antirejection drugs, including but not limited to mycophenolate, tacrolimus, sirolimus, cyclosporine, and azathioprine, are permitted.

- Medication other than that described as prohibited in Section 10.8.6.7.1 required for treatment of pre-existing conditions or acute illness is permitted.

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

- 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.

10.8.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal for Substudy B

See Section 7.

10.8.8. Study Assessments and Procedures for Substudy B

Refer to Section 8 and the following subsections:

- Section 8.1 Administrative and Baseline Procedures
- Section 8.1.1 Telehealth Visits

10.8.8.1. Immunogenicity Assessments

10.8.8.1.1. RSV Vaccine Antibody Testing

Refer to Section 8.2.3 for general information regarding use and storage of biological samples.

Blood samples (approximately 20 mL per sample) will be collected from participants for immunogenicity testing as specified in the study-specific SoA (refer to Section 10.8.1.3). The total blood sampling volume for individual participants in Substudy B is approximately 60 mL.

RSV A– and RSV B–neutralizing antibody titers will be measured for each blood sample at each time point, and reported as the NTs.

Blood 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.

10.8.8.2. 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.

Refer to Section 8.3 and the following subsections:

- Section 8.3.1 Physical Examinations
- Section 8.3.2 Vital Signs
- Section 8.3.3 Clinical Safety Laboratory Assessments
- Section 8.3.4 Electronic Diary for Reactogenicity

E-diary assessments are included in Substudy B for participants' reporting of local reactions and systemic events for 7 days from the day of each administration of the study intervention. Participants will receive reminders to complete the vaccination e-diary on a daily basis, starting on the day of vaccination (Day 1) through Day 7 after each vaccination. Refer to Section 8.3.4 for details.

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

Refer to Section 8.4 and the following subsections:

- Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information
- Section 8.4.2 Method of Detecting AEs and SAEs
- Section 8.4.3 Follow-Up of AEs and SAEs
- Section 8.4.4 Regulatory Reporting Requirements for SAEs
- Section 8.4.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
- Section 8.4.6 Cardiovascular and Death Events
- Section 8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs
- Section 8.4.8 Adverse Events of Special Interest
- Section 8.4.9 Medical Device Deficiencies
- Section 8.4.10 Vaccination Errors

10.8.8.4. Substudy B Procedures

10.8.8.4.1. Visit 201 – Vaccination 1 (Clinic, Day 1)

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

The investigator or his or her 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 study intervention administration** 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 full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record any medical history of clinical significance, including:
  - Heart disease;
  - Lung disease;
  - Asthma;
  - Diabetes mellitus/metabolic disease;
  - Liver disease;
  - Renal disease;
  - Neurologic disease;
  - Hematologic disease;
  - History and type of SOT;
  - Oncology history;
  - Autoimmune inflammatory disorders.
  - In addition, for specific criteria for participants with known stable infection with HIV, please refer to Section 10.6, Appendix 6.
- Obtain and record current/former tobacco usage.
- Perform a clinical assessment, including baseline respiratory rate. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Obtain details of any nonstudy vaccinations, and prohibited medications and concomitant treatments as described in Section 10.8.6.7.

- Collect ongoing oral corticosteroids, chemotherapy, immunotherapy, immunomodulator/biologic treatments, and immunosuppressive regimens as well as those received (and/or discontinued) within the last 3 months.
- **Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.**
- 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 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.
- Qualified site staff member(s) will administer a single dose of study intervention into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IPM for further 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 AE page of the CRF, and on an SAE form as applicable.
- Explain the e-diary technologies available for this study (see Section 8.3.4) and assist the participant in downloading the study application onto his or her 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, with Day 1 being the day of vaccination.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Ask the participant to contact the site staff or investigator immediately if he/she 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 (as detailed in Section 8.10):
  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring >20 measuring device units (greater than 10 cm).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Remind the participant that study staff may contact him or her to obtain additional information on events entered into the e-diary.
- Remind participants to inform the study staff of any AEs, AESIs, SAEs, and NDCMCs that occur for the duration of the trial as described in Section 8.4.
- Remind the participant to bring the e-diary to the next 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.

10.8.8.4.2. Visit 202 – Vaccination 2 (Clinic, 28 to 35 Days After Vaccination at Visit 201)

- Obtain details of any nonstudy vaccinations, and prohibited medications and concomitant treatments as described in Section 10.8.6.7.
- Collect oral corticosteroids, chemotherapy, immunotherapy, immunomodulator/biologic treatments, and immunosuppressive regimens.
- Ensure and document that the participant is still eligible for vaccination and that all the inclusion criteria and none of the exclusion criteria are met.
- 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 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.

- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF. Any ongoing reactions must be assessed at the next contact.

- Qualified site staff member(s) will administer a single dose of study intervention into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IPM for further 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 AE page of the CRF, and on an SAE form as applicable.

- Remind participant how to complete the reactogenicity e-diary and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he/she 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 (as detailed in Section 8.10):

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring >20 measuring device units (greater than 10 cm).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Remind the participant that study staff may contact him or her to obtain additional information on events entered into the e-diary.

- Remind participants to inform the study staff of any AEs, AESIs, SAEs, and NDCMCs that occur for the duration of the trial as described in Section 8.4.

- Remind the participant to bring the e-diary to the next 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.

10.8.8.4.3. Visit 203 – 1-Month Follow-Up (Clinic, 28 to 35 Days After Vaccination at Visit 202)

- Obtain details of any nonstudy vaccinations, and prohibited medications and concomitant treatments as described in Section 10.8.6.7.
- Collect oral corticosteroids, chemotherapy, immunotherapy, immunomodulator/biologic treatments, and immunosuppressive regimens.
- Collect a blood sample of approximately 20 mL.
- Review the participant's e-diary data. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF. Any ongoing reactions must be assessed at the next contact.
- Collect the provisioned device or assist the participant with removing the study application from his or her own personal device.
- Record AEs, AESIs, SAEs, and NDCMCs as described in Section 8.4.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

10.8.8.4.4. Visit 204 – 6-Month Safety Follow-Up (Telephone or Clinic, Within 175 to 189 Days After Vaccination 2 at Visit 202)

- Contact the participant by telephone. This visit can be conducted as a clinic visit if the investigator deems it is necessary for the participant to be seen in person.
- Obtain details of any nonstudy vaccinations, and prohibited medications and concomitant treatments as described in Section 10.8.6.7.
- Collect oral corticosteroids, chemotherapy, immunotherapy, immunomodulator/biologic treatments, and immunosuppressive regimens.
- Review ongoing reactogenicity e-diary symptoms reported as present on the last day of the e-diary and obtain stop dates. Record stop dates in the CRF if required.
- Record AESIs, SAEs, and NDCMCs as described in Section 8.4.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

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

See Section 8.10.

10.8.9. Statistical Considerations for Substudy B

See Section 9 for the general protocol statistical considerations and see substudy-specific statistical considerations below.

10.8.9.1. Statistical Hypotheses

Substudy B is descriptive, without any hypothesis testing. Immunogenicity data will be descriptively summarized for this substudy and may be descriptively compared with other study results.

10.8.9.1.1. Estimands

The estimands corresponding to each primary, secondary, and exploratory objective (if any) are described in Section 10.8.3.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (Section 10.8.9.2). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing immunogenicity results will not be imputed, as MCAR is assumed.

10.8.9.1.2. Multiplicity Adjustment

No multiplicity adjustment will be applied for this substudy.

10.8.9.2. Analysis Sets

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

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

Defined Analysis Set	Description
Evaluable immunogenicity population	This population will be defined for Substudy B and it includes all participants who meet the following criteria: • Are eligible for Substudy B; • Received 2 doses of study intervention; • Have the 1-month postvaccination (1 month after last dose) blood collection within an appropriate window; • Have at least 1 valid and determinate assay result 1 month after vaccination (1 month after last dose); • Have no major protocol violations from vaccination through the 1-month postvaccination blood draw (1 month after last dose).
mITT immunogenicity population	All participants in this substudy who received study intervention and had at least 1 valid and determinate assay result at any time point after receiving study intervention.

10.8.9.3. Statistical Analysis

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.

10.8.9.3.1. General Considerations

See Section 9.3.1 for general considerations of the statistical analyses.

10.8.9.3.2. 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. 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 each 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).

Table 8. Primary Endpoint Analyses

Endpoint	Statistical Analysis Methods
	• AEs and SAEs will be categorized according to MedDRA terms. All of the AEs within 1 month after each vaccination and the AESIs, SAEs, and NDCMCs throughout the study will be descriptively summarized with counts, percentages, and associated Clopper-Pearson 95% CIs (Section 9.3.1.1). • A 3-tier approach will be used to summarize AEs. (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 PT is defined as a Tier 2 event if there are at least 1% of participants in any vaccine group reporting the event, in any age stratum. As there is no placebo group in this substudy, Tier 2 event analysis is not defined. (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. • For Tier 1 events, the 95% CIs for the difference in the percentage of participants reporting the events between the RSVpreF group from this substudy and a control will be calculated using the test statistic proposed by Miettinen and Nurminen. In addition, for Tier 1 events, the asymptotic p-values will be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. The control will be defined in the SAP.
Immunogenicity	• GMTs at each applicable blood sampling visit will be descriptively summarized with 2-sided 95% CIs for both RSV A and RSV B NT subgroups (Section 9.3.1.2.1). • GMFRs from before vaccination to each postvaccination blood sampling visit will be descriptively summarized with 95% CIs for both RSV A and RSV B NT subgroups (Section 9.3.1.2.2). • GMTs and GMFRs may also be summarized for each age stratum (18 to <60 years of age and ≥60 years of age).

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

Not applicable.

10.8.9.4. Interim Analysis

No interim analysis is planned.

10.8.9.4.1. Analysis Timing

As Substudy B is open-label, data may be summarized on an ongoing basis for decision-making.

10.8.9.5. Sample Size Determination

Substudy B enrollment is not based on statistical criteria.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALK	anaplastic lymphoma kinase
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BRAF	B-type Raf proto-oncogene
CBER	Center for Biologics Evaluation and Research (United States)
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTIS	Clinical Trial Information System
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding

Abbreviation	Term
e-diary	electronic diary
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
eICD	electronic informed consent document
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
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
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
IVIG	intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
LLOQ	lower limit of quantitation
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
LS	least square
MCAR	missing completely at random
MDR	medical device regulation

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition factor receptor
mITT	modified intent-to-treat
MQI	medically qualified individual
mRNA	messenger ribonucleic acid
MTX	methotrexate
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non–small-cell lung cancer
NT	neutralizing titer
NT50	50% neutralizing titer
NTRK	neurotrophic tyrosine receptor kinase
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	prefilled syringe
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTLD	posttransplant lymphoproliferative disorder
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RET	rearranged during transfection
ROS1	c-ros oncogene 1
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
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCIG	subcutaneous immunoglobulin
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SOT	solid organ transplant
SRSD	single reference safety document

Abbreviation	Term
SUSAR	suspected unexpected serious adverse reaction
T bili	total bilirubin
TNFa	tumor necrosis factor alpha
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect

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Signed By:	Date(GMT)	Signing Capacity
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