A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF 3 LOTS OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN HEALTHY ADULTS

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Brief Title: Clinical Lot Consistency for RSVpreF in a Population of Healthy Adults 18 to ≤49 Years of Age

Document History

Document	Version Date
Protocol amendment 1	08 Feb 2022
Original protocol	23 August 2021

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 (08 Feb 2022)

Overall Rationale for the Amendment: Increasing the overall sample size of the study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 4.1 Overall Design, and 9 Statistical Considerations	Sample size was increased and the estimated enrollment period was removed. Statistical methods, including sample size and power calculations, were updated.	In response to CBER feedback.
2.2.1 Clinical Overview	RSV program study details were updated.	To include the latest data.
4.2.2 Diversity of Study Population	The study number was corrected.	To correct a typographical error.
9.3.2 Primary Endpoint(s)	The definition of a Tier 2 event was updated.	To align with other studies within the program.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Clinical Lot Consistency for RSVpreF in a Population of Healthy Adults 18 to ≤49 Years of Age

Indication

Pfizer's RSV stabilized prefusion F subunit vaccine (RSVpreF) is a prophylactic vaccine that is being developed for 2 indications:

- **Maternal:** Prevention of LRTI-RSV in infants by active immunization of pregnant women.
- **Older Adult:** Prevention of RSV-associated msLTRI in adults 60 years of age and older via active immunization.

Rationale

As of June 2021, RSVpreF has been studied in 3 completed and 3 ongoing clinical trials in healthy adults and pregnant women. RSVpreF was shown to be well tolerated, with an acceptable safety profile, and was highly efficacious in the RSV human challenge model (Section 2.2.1).

This study will examine 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 to demonstrate lot equivalence in manufacturing of RSVpreF. Additionally, the study will contribute data supporting the development of RSVpreF as a prophylactic vaccine against RSV disease in infants through maternal immunization and in older adults through active vaccination.

Objectives, Estimands, and Endpoints

Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity		
To demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination are equivalent.	• The ratio of neutralizing GMTs obtained 1 month after vaccination for every pair of RSVpreF lots (Group 1/Group 2, Group 1/Group 3, Group 2/Group 3) for RSV A and RSV B neutralization assays, in participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable participants).	• RSV A and RSV B NTs.
Primary Safety		
To evaluate the safety and tolerability profiles of 3 RSVpreF lots (Groups 1, 2, and 3).	• The incidence rate of each safety outcome in participants receiving 1 dose of the study intervention, estimated by the percentage of participants reporting the event among those who receive study intervention, in the pooled RSVpreF lots and placebo.	• Local reactions (redness, swelling, and pain at the injection site) self-reported on e-diaries for 7 days after vaccination. • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) self-reported on e-diaries for 7 days after vaccination. • AEs from the day of consent through study completion. • SAEs from the day of consent through study completion.


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Overall Design

Brief Summary

This Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study will be conducted in the US.

Healthy adults 18 to ≤49 years of age will be enrolled and randomized in a 1:1:1:1 ratio to receive 1 of 3 lots of RSVpreF (Group 1: Group 2: Group 3) or placebo.

There are 2 scheduled study visits 1 month apart. Participants will have blood samples for immunogenicity assessments collected both prior to vaccination (Visit 1) and 1 month after vaccination (Visit 2).

Local reactions (redness, swelling, and pain at the injection site) occurring at the RSVpreF or placebo injection site and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) occurring within 7 days after vaccination will be prompted for and collected daily by the participant in an e-diary device or smartphone application.

AEs and SAEs will be collected from the signing of informed consent through study completion (Visit 2).

Number of Participants

Up to 1000 participants will be enrolled in the study. Allowing for a nonevaluable rate of approximately 10%, this will provide the required sample size of approximately 900 participants for the evaluable population analysis. Participants who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

Intervention Groups and Duration

There will be 4 study groups: Group 1, Group 2, Group 3 (representing 3 RSVpreF manufacturing lots), and placebo. Up to 1000 participants will be randomly assigned in a 1:1:1:1 ratio so that each group numbers approximately 250 participants. Each randomized participant will receive his or her vaccine assignment, administered as a single IM injection into the deltoid muscle (nondominant arm preferred) at Visit 1. Participants and study personnel will be blinded to intervention groups and assignments.

The last study visit for each participant will be approximately 1 month after vaccination.

Statistical Methods

Equivalence of the 3 RSVpreF lots will be assessed by using 2-sided 95% CIs for ratios of lot-specific GMTs. Equivalence will be declared using a 1.5-fold criterion, ie, that the 95% CI for the ratio of GMTs for every pair of RSVpreF lots must be contained in the interval (0.667, 1.5), for both antigens simultaneously. CIs will be derived by calculating differences in means and CIs for natural log titers (based on the t-distribution) and then exponentiating the results.

Safety will be summarized using counts, percentages, and incidences of local reactions, systemic events, AEs, and SAEs. Incidence rates of local reactions, systemic events, AEs, and SAEs after vaccination in the combined RSVpreF group relative to the incidence rates in the placebo group will be reported.

1.2. Schema

Healthy Adults 18 to ≤49 Years of Age		**Visit 1** *Day 1: Vaccination*		**Visit 2** *1-Month Follow-Up*
Randomization Ratio	Randomized (n)			
1	250	RSVpreF Group 1[a]	1 Month	RSVpreF Group 1
1	250	RSVpreF Group 2[a]		RSVpreF Group 2
1	250	RSVpreF Group 3[a]		RSVpreF Group 3
1	250	Placebo[b]		Placebo
		• Blood sampling • Vaccination • Safety assessments		• Blood sampling • Safety assessments

a. RSVpreF Groups 1 through 3 are administered a 120-µg dose of 1 of 3 RSVpreF manufacturing lots.
b. The placebo group is administered a matching volume containing excipients reconstituted in sterile water for injection, containing no RSVpreF antigens.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to Study Assessments and Procedures in Section 8 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.

Visit Identifier	**Visit 1**	**Visit 2**
Visit Description	**Vaccination**	**1-Month Follow-Up**
Visit Window	**Day 1**	**28 to 35 Days After Visit 1**
Type of Visit	**Clinic**	**Clinic**
Obtain informed consent	X	
Obtain participant number via IRT	X	
Obtain demography and medical history data	X	
Perform clinical assessment (and physical examination and vital signs if deemed necessary)	X	
Obtain prevaccination temperature (body)	X	
Confirm negative urine (or serum) pregnancy test (for WOCBP)	X	
Discuss contraceptive use (as appropriate)	X	
Record nonstudy vaccinations	X	X
Review concomitant medication use	X	X
Review inclusion and exclusion criteria and confirm eligibility	X	
Review temporary delay criteria	X	
Obtain blood sample for antibody assessment	~20 mL[a]	~80 mL
Obtain randomization number and product kit assignment from IRT	X	
Assist with app download or issue e-diary, issue measuring device and digital thermometer; provide e-diary training	X	
Study intervention administration	X	
Postvaccination observation (30 minutes) and acute immediate reaction assessment	X	
Provide study participant with emergency contact card	X	
Review e-diary data (daily review during the 7 days following vaccination)	X	
Review e-diary for ongoing reactogenicity, obtain stop dates, collect e-diary		X
Record adverse events and serious adverse events and obtain any missing stop dates	X	X

Abbreviations: IRT = interactive response technology; WOCBP = women of childbearing potential.

a. Blood sample must be collected before vaccination.

2. INTRODUCTION

Pfizer is currently developing a vaccine, RSVpreF, for the prevention of RSV-associated LRTI, protecting infants by maternal immunization during pregnancy and protecting adults 60 years of age and older via direct immunization.

RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in those with risk factors, including premature infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems.[1] However, most cases of RSV disease occur in healthy, full-term infants without risk factors.[2] Worldwide, RSV kills approximately 118,200 children annually, with about half of those deaths occurring in infants under 6 months of age, and the majority of those occurring in resource-limited countries.[3,4] In the US, RSV is the leading cause of infant hospitalization, with more than 60,000 hospitalizations of children 12 months of age and younger annually.[5,6] There is increasing evidence that the link between severe RSV disease in infancy and wheezing later in childhood may be causal.[7,8] Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall.[9] Infection is essentially universal by the time children reach 2 years of age.[10]

No specific treatments for RSV exist, and available prophylactic measures (ie, RSV monoclonal antibody) are limited to use in only those infants at highest risk; additionally, in LMICs, use of available RSV prophylaxis is cost-prohibitive.[11,12] While active immunization against RSV in infants might be an option, multiple efforts extending over half a century to develop a safe and effective RSV vaccine to protect infants from disease have yielded little success. The early peak of disease presents a further obstacle to an active vaccination strategy for infants. Given these challenges, maternal immunization to protect infants early in life offers an attractive strategy for infant disease prevention.

In addition to infants and young children, 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.[13] 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.[14] Current epidemiology shows that RSV is responsible for approximately 177,000 hospitalizations and 14,000 deaths annually in US adults 65 years of age and older.[13] 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.[15] In the US, RSV disease incidence rates in older adults are approximately half those of influenza, with variation year to year.[16] 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 infection).[17,18] However, the burden of adult RSV disease could be underestimated since testing for RSV is less common in older adults than in children. RSV disease in adults is also difficult to diagnose based on clinical signs and symptoms alone, and, prior to the broader use of more

sensitive detection methods, laboratory confirmation of RSV in adults was challenging because of low levels of virus shedding.[14]

RSV disease management in adults is limited to supportive measures such as hydration and oxygenation. Aerosolized ribavirin has limited evidence of effectiveness and is predominantly restricted to hospitalized severely immunocompromised patients, because of inconvenient administration, teratogenicity and anemia concerns, and high cost, making vaccination a high priority.[18,19]

2.1. Study Rationale

The study will contribute data to support the development of RSVpreF as a prophylactic vaccine against severe clinical RSV disease in infants through maternal immunization and in older adults through preventive vaccination.

To demonstrate equivalence in manufacturing of RSVpreF, this study will examine 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.

2.2. Background

The vaccine investigated in this study is a bivalent RSV prefusion F subunit vaccine 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:

- **Maternal:** Prevention of LRTI-RSV in infants by active immunization of pregnant women.
- **Older Adult:** Prevention of RSV-associated msLRTI in adults 60 years of age and older via active immunization.
- As of June 2021, RSVpreF has been studied in 3 completed and 3 ongoing clinical trials in healthy adults and pregnant women. RSVpreF was shown to be well tolerated, with an acceptable safety profile, and highly efficacious in the human challenge model (Section 2.2.1).

2.2.1. Clinical Overview

Maternal Program Studies

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

- C3671003 is a completed Phase 2b multicenter, randomized, placebo-controlled study in up to 650 healthy pregnant women 18 through 49 years of age who received RSVpreF at 120 µg and 240 µg, formulated with or without $Al(OH)_3$, or placebo. CCI [redacted]

- C3671004 is a completed Phase 2b study of 713 healthy nonpregnant women 18 through 49 years of age. A total of 709 participants received 120 µg RSVpreF or 240 µg RSVpreF with $Al(OH)_3$ or placebo, administered with or without concomitant Tdap. The study demonstrated a good safety and tolerability profile, high immune responses, and noninferiority of the responses to RSVpreF when coadministered with Tdap, with RSV A and RSV B 50% NT GMRs of 0.97 and 0.96 at 1 month after vaccination.

- C3671008 is an ongoing Phase 3 study designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended LRTI in infants. Healthy women ≤49 years of age who are between 24 and 36 weeks of gestation receive either RSVpreF 120 µg or placebo. CCI [redacted]

Adult Program Studies

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

- In the Phase 1/2 study (C3671001), 1233 healthy adults 18 through 49 and 50 through 85 years of age received the 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg), with or without $Al(OH)_3$, or placebo, administered with or without concomitant influenza vaccine. The results have shown that the vaccine was well tolerated and immunogenic in both age groups. RSVpreF elicited robust neutralizing responses against RSV A and RSV B 1 month after vaccination for both age groups across all vaccine dose levels and formulations; these responses remained high through the 12 months after vaccination. In 616 vaccinated participants in the 50- through 85-year age group, RSV 50% NT GMFRs were high across all arms, ranging from 9 to 13 from before vaccination to 1 month after vaccination and from 3 to 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 investigational vaccine.

- Phase 1/2 study C3671002, in 250 older adults 65 through 85 years of age, studied the 3 dose levels of RSVpreF with $Al(OH)_3$, or $CpG/Al(OH)_3$ (60 µg, 120 µg, and 240 µg), given as a single dose or on a schedule of 2 doses administered 2 months apart. All RSVpreF doses and formulations elicited high RSV A and RSV B neutralizing antibody GMTs 1 month after vaccination (GMFRs ranging from 4.8 to 11.6 and 4.5 to 14.1, respectively). CpG-containing formulations did not further increase neutralizing GMTs compared to RSVpreF with or without $Al(OH)_3$. GMTs in all groups declined, but remained higher than baseline (before vaccination) and placebo (SIIV only) 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.

- *A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of a Respiratory Syncytial Virus Vaccine (RSVpreF) in a Virus Challenge Model in Healthy Adults* (NCT04785612) was conducted by hVIVO in 70 healthy participants 18 to 50 years of age. Participants received a single dose of either 120 µg RSVpreF or placebo, and 4 weeks later underwent intranasal challenge with RSV-A Memphis 37b virus. The immunogenicity and efficacy of RSVpreF vaccination on virus replication, clinical symptoms, and incidence of symptomatic RSV infection 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.

- C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety, immunogenicity, and efficacy of Pfizer's RSVpreF in prevention of RSV-associated msLRTI in adults 60 years of age and older during the first RSV season and the long-term immunogenicity and efficacy of RSVpreF across multiple RSV seasons. Both healthy adults and adults with stable chronic diseases are included. Approximately 10% of participants with stable chronic cardiopulmonary conditions such as COPD, asthma, or CHF are being enrolled. CCI [redacted]

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): RSVpreF		
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines[20] as well as RSVpreF. The most common events reported in the FIH C3671001 study were mild to moderate pain at the injection site, fatigue, headache, and muscle pain.	• 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.
Safety profile of a novel vaccine close to being, but not yet fully, characterized.	Data available from completed and ongoing studies showed a low incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, and race/ethnicity.	• Collection and review of AEs and SAEs throughout the study. • All participants will be observed for at least 30 minutes after vaccination.
Theoretical risk for RSV enhancement.	RSVpreF is being evaluated in ongoing clinical studies. Pfizer's immunization approach circumvents the risk of vaccine-mediated disease enhancement that was observed in the 1960s following direct immunization of RSV-naive infants with an FI-RSV. FI-RSV elicited a predominantly nonneutralizing antibody response and a Th2-biased cell-mediated response, both of which are considered potential contributing factors to disease enhancement. During preclinical studies, in a standard cotton rat infectious RSV challenge model, FI-RSV showed pathological signs of causing disease enhancement, and the current Pfizer vaccine candidate, RSVpreF, did not. Most important, RSV vaccine-mediated disease enhancement has not been reported to occur in RSV-experienced individuals after vaccination with any RSV vaccine candidate. Because older adults are universally RSV-experienced, they are not considered at risk for a disease-enhancing immune response to the vaccine that could exacerbate infection in themselves.	• Collection and review of AEs and SAEs throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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.
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	• Pfizer will work with sites to ensure appropriate COVID-19 prevention strategies.

2.3.2. Benefit Assessment

Benefit considerations may include:

- Potential benefit of receiving study intervention that may have clinical utility in the future.
- Contributing to the process of developing new therapies in an area of unmet need.
- Medical evaluations/assessments associated with study procedures.

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 healthy participants and older participants who may be at risk of RSV.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity		
To demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination are equivalent.	• The ratio of neutralizing GMTs obtained 1 month after vaccination for every pair of RSVpreF lots (Group 1/Group 2, Group 1/Group 3, Group 2/Group 3) for RSV A and RSV B neutralization assays, in participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable participants).	• RSV A and RSV B NTs.

Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety		
To evaluate the safety and tolerability profiles of 3 RSVpreF lots (Groups 1, 2, and 3).	• The incidence rate of each safety outcome in participants receiving 1 dose of the study intervention, estimated by the percentage of participants reporting the event among those who receive study intervention, in the pooled RSVpreF lots and placebo.	• Local reactions (redness, swelling, and pain at the injection site) self-reported on e-diaries for 7 days after vaccination. • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) self-reported on e-diaries for 7 days after vaccination. • AEs from the day of consent through study completion. • SAEs from the day of consent through study completion.
CCI [redacted]		

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study will be conducted in the US. Up to 1000 healthy women and men 18 to ≤49 years of age will be enrolled.

There are 2 scheduled study visits. Participants will have blood samples for immunogenicity assessments collected both prior to vaccination (Visit 1) and 1 month after vaccination (Visit 2).

Local reactions (redness, swelling, and pain at the injection site) occurring at the RSVpreF or placebo injection site and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) occurring within 7 days after vaccination will be prompted for and collected daily by the participant in an e-diary device or smartphone application.

AEs and SAEs will be collected from the signing of informed consent through Visit 2.

Number of Participants

Up to 1000 participants will be enrolled in the study. Allowing for a nonevaluable rate of approximately 10%, this will provide the required sample size of approximately 900 participants for the evaluable population analysis. Participants who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

Intervention Groups and Duration

There will be 4 study groups: Group 1, Group 2, Group 3 (representing 3 RSVpreF manufacturing lots), and placebo. Up to 1000 participants will be randomly assigned in a 1:1:1:1 ratio so that each group numbers approximately 250 participants. Each randomized participant will receive his or her vaccine assignment, administered as a single IM injection into the deltoid muscle (nondominant arm preferred) at Visit 1. Participants and study personnel will be blinded to intervention groups and assignments.

The last study visit for each participant will be approximately 1 month after vaccination.

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.2.1. Choice of Contraception/Barrier Requirements

There is no suspicion of human teratogenicity based on the intended pharmacology of the compound; however, human reproductive safety data are limited for RSVpreF. Therefore, the use of a highly effective method of contraception is required (see Section 10.3).

4.2.2. Diversity of Study Population

To the extent possible, recruitment attempts will be made to enroll participants so that the study demographic profile approximates the general population. Reasonable attempts will be made to enroll participants with the distribution of characteristics shown below:

Race	**US Census Data[21] Target for C3671014**
Black or African American	13.4%
Asian	5.9%
American Indian or Alaska Native	1.3%
Native Hawaiian or other Pacific Islander	0.2%
White	76.3%
Ethnicity	**US Census Data Target for C3671014**
Hispanic or Latino(a) or of Spanish origin	18.5%

4.3. Justification for Dose

The final dose and formulation of RSVpreF selected for use in this study is based on the safety and immunogenicity data from 3 Phase 1/2 studies and the efficacy evaluation in the human challenge study.

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

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

- A study in pregnant women 18 through 49 years of age evaluated the safety, tolerability, and immunogenicity of 120-µg and 240-µg RSVpreF dose levels with and without $Al(OH)_3$ (C3671003).

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

Based on the Phase 1/2 studies (C3671001 and C3671002), no substantial differences were observed between the immunogenicity or reactogenicity of 120-µg and 240-µg dose levels or of formulations with and without $Al(OH)_3$ or CpG/$Al(OH)_3$. Therefore, the 120-µg without-$Al(OH)_3$ formulation was chosen for the human challenge study. The acceptable reactogenicity and safety profile along with the high efficacy demonstrated in the

primarily-upper-respiratory-tract and mild-to-moderate disease human challenge model led to selection of 120 µg for the RSV Phase 3 studies.

4.4. End of Study Definition

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

A participant is considered to have completed the study when she/he has completed all study visits and procedures.

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. Use of a prescreener for study recruitment purposes will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Healthy males or nonpregnant, nonbreastfeeding females between the ages of 18 and ≤49 years, inclusive, at Visit 1 (Day 1).

   Refer to Appendix 3 for reproductive criteria for male (Section 10.3.1) and female (Section 10.3.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with scheduled visits, laboratory tests, lifestyle considerations, and other study procedures, including daily completion of the e-diary for 7 days after study vaccination.

3. Healthy participants as determined by medical history, physical examination (if required), and the clinical judgment of the investigator to be eligible for inclusion in the study. Participants with preexisting chronic medical conditions determined to be stable in the clinical judgment of the investigator may be included.

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Bleeding diathesis or condition associated with prolonged bleeding time that may contraindicate IM 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 or any related vaccine.

3. Unstable chronic medical condition or disease requiring significant change in therapy[a] or hospitalization for worsening disease within 3 months before receipt of study intervention.

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

5. Known infection with HIV, HCV, or HBV.

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.

Prior/Concomitant Therapy:

7. Previous vaccination with any licensed or investigational RSV vaccine at any time prior to enrollment or planned receipt throughout the study.

8. Receipt of any blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

[a] A change to a new therapy category is considered significant if caused by worsening disease. A change in dose or therapy within a therapy category (eg, change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) is not considered significant.

9. Receipt of monoclonal antibodies from 60 days before study intervention administration or planned receipt throughout the study.

10. Receipt of systemic treatment with known immunosuppressant medications within 60 days before study intervention administration or the use of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days within 28 days prior to study enrollment. Prednisone use of <20 mg/day for <14 days is permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, ears) corticosteroids are permitted.

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

12. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8.

Prior/Concurrent Clinical Study Experience:

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

Other Exclusions:

14. Pregnant females; breastfeeding females; and WOCBP who are unwilling or unable to use a highly effective method of contraception as outlined in the protocol for the duration of the study.

15. Men who are unwilling to comply with contraception methods as outlined in the protocol for the duration of the study.

16. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and partner(s) from the permitted list of contraception methods (see Appendix 3, Section 10.3.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call

immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

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

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

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

- Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before study intervention administration.

- Receipt of any inactivated vaccine or any seasonal or pandemic influenza vaccine (whether inactivated or LAIV), licensed COVID-19 vaccines, or COVID-19 vaccines authorized for temporary or emergency use within 14 days or any live vaccine within 28 days before study intervention administration.

- Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to the RSVpreF and placebo (lyophilized cake containing excipients reconstituted in sterile water for injection, containing no RSVpreF antigens).

6.1. Study Intervention(s) Administered

Intervention Name	RSVpreF
Type	Vaccine.
Dose Formulation	The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The 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 intended vaccine dose is delivered by injecting the entire contents of the syringe.
Dosage Level(s)	120 µg RSVpreF by single injection once only.
Route of Administration	IM injection into the deltoid muscle of the nondominant arm (preferred).
Use	Experimental.
Sourcing	RSVpreF will be provided by the sponsor to each study site.
Packaging and Labeling	The vaccine will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

Intervention Name	Placebo
Type	Placebo.
Dose Formulation	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. It contains no antigens. The placebo will be reconstituted by a diluent consisting of sterile water in a PFS. The lyophilized cake contains excipients that, after reconstitution, will yield a volume matching the RSVpreF. The fill volume of the placebo vial and diluent PFS is delivered by injecting the entire contents of the syringe.
Dosage Level(s)	N/A
Route of Administration	IM injection into the deltoid muscle of the nondominant arm (preferred).
Use	Placebo control.
Sourcing	Placebo will be provided by the sponsor to each study site.
Packaging and Labeling	The vaccine will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at the vaccination visit (Day 1) in accordance with the study's SoA. The study intervention will be administered intramuscularly by injecting the entire contents of the syringe into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Study intervention administration will be performed by appropriately designated blinded study staff at the investigator site.

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

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

Study intervention administration details will be recorded on the CRF and pharmacy/study records.

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), a PFS containing sterile water, and a vial adapter.

Instructions for medical device use are provided in the IP manual.

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

Please refer to Section 8.3.9 for details.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations

must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

5. Study interventions should be stored in their original containers.

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

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. 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 IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately medically 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. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

Study intervention will be dispensed and administered at study Visit 1 summarized in the SoA.

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

6.3.2. Blinding Arrangements

The study is double-blind.

6.3.2.1. Blinding of Study Site Personnel

The participant, study coordinator, and all site staff will be blinded.

Please refer to the IP manual for further details.

6.3.2.2. Blinding of the Sponsor

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

6.3.3. 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 sponsor 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 IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are vaccinated at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of vaccination will be recorded in the source documents and in the CRF. The study intervention identification details and study participant identification will be checked and confirmed at the time of and prior to administration by a second member of the study site staff who is not the person administering the vaccine.

The site will complete the required vaccine Preparation Record located in the IP manual. 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.

6.5. Dose Modification

This section is not applicable.

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

No intervention will be provided to study participants at the end of their study participation.

6.7. 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 medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
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.**

6.8. Concomitant Therapy

6.8.1. Prohibited Concomitant Vaccinations and Medications

- Licensed or nonstudy investigational RSV vaccines are prohibited at any time prior to enrollment and thereafter during the course of the study.

- Investigational vaccines and investigational drugs are prohibited within 28 days prior to enrollment and at any time during the study.

6.8.2. Withholding Periods for Concomitant Vaccinations and Medications

Unless considered medically necessary, the following restrictions apply to nonstudy licensed vaccines and medications as well as COVID-19 vaccines authorized for temporary or emergency use:

- COVID-19 vaccines may not be given within 14 days before or within 7 days after study intervention administration.

- Nonstudy inactivated vaccines or seasonal or pandemic influenza vaccine (whether inactivated or LAIV) may not be given within 14 days before or within 7 days after study intervention administration.

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

- Systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days should not be given within 28 days before study intervention administration through the conclusion of study participation.

- Chronic systemic treatment with known immunosuppressant medications should not be given within 60 days before study intervention administration through the conclusion of study participation.

- Monoclonal antibodies should not be given within 60 days before study intervention administration through the conclusion of study participation.

- Blood/plasma products or immunoglobulin should not be given within 60 days before study intervention administration through the conclusion of study participation.

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

6.8.3. Permitted Nonstudy Vaccines and Medications During the Study

The following restrictions apply to permitted vaccines and medications (except when they are considered medically necessary):

- Licensed or authorized COVID-19 vaccines may be given during the study starting 7 days after study intervention administration (Day 8).

- Nonstudy inactivated vaccines and seasonal or pandemic influenza vaccine (whether inactivated or LAIV) may be given on Day 8, where Day 1 is the day of study intervention administration.

- Nonstudy live vaccines may be given starting 28 days after study intervention administration (Day 29).

- Inhaled/nebulized, intra-articular, intrabursal, or topical (eg, skin, eyes) corticosteroids are permitted. Short-term use of systemic corticosteroids (equivalent of <20 mg/day of prednisone) for <14 days prior to the administration of study intervention is permitted.

- The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration is permitted.

- Medication other than that listed in Section 6.8.1 and Section 6.8.2 required for treatment of preexisting stable conditions is permitted.

6.8.4. Recording Nonstudy Vaccinations and Concomitant Medications

Receipt of the following concomitant medications and vaccinations will be recorded in the CRF:

- All nonstudy vaccinations received from 28 days prior to study enrollment through the conclusion of study participation.

- The following medications, although prohibited (Section 6.8.1), will be collected from Visit 1 to the end of the study if required for medical care:

  - Immunosuppressant medications.

  - Monoclonal antibodies.

  - Systemic corticosteroids, ie, oral, IM, or IV. Do not record topical, optic, otic, inhaled, intra-articular, or intrabursal corticosteroids.

  - Blood/plasma products or immunoglobulin.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

7.1.1. Pregnancy

As this is a single-dose study, in the case of a positive confirmed pregnancy after vaccination, the participant may remain in the study and complete study procedures. Any pregnancy confirmed prior to randomization will deem the participant as a screen failure.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for withdrawal from the study may include the following:

- Refused further study procedures
- Lost to follow-up
- Death
- Study terminated by sponsor
- Adverse events
- Physician decision
- Protocol deviation
- Participant request

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

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

If a participant withdraws from the study, he/she 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Vaccine SAE Reporting Form.

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

Participants who withdraw after randomization will not be replaced.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her 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 study procedures and/or postvaccination study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to 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, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

All screening evaluations must be completed and reviewed to confirm that potential 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 may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Efficacy Assessments

Efficacy assessments are not applicable to this study.

8.1.2. Immunogenicity Assessments

8.1.2.1. Blood Collection

Blood samples for immunogenicity assessments will be collected from all enrolled participants prior to study vaccination at Visit 1 (approximately 20 mL per sample) and at Visit 2 (1 month after Visit 1) (approximately 80 mL per sample).

Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time of each sample will be recorded.

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

8.1.2.2. RSV Vaccine Antibody Testing

Serum samples will be assayed for RSV A and RSV B serum NTs [redacted]

RSV A and RSV B serum NTs will be determined and reported as the NT. CCI [redacted]

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

CCI [redacted]

8.1.3. Biological Samples

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

The participant may request that his/her 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 sequencing of the participant's DNA is performed.

8.2. Safety Assessments

Participants will be observed for 30 minutes after vaccination and any reactions occurring during that time will be recorded as AEs.

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

8.2.1. Physical Examinations

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

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

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Section 10.2) must be reported according to the processes in Section 8.3.1 to Section 8.3.3.

8.2.2. Vital Signs

The participant's body temperature will be assessed prior to vaccination.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, vital signs should also be evaluated. Record any findings in the source documents and, if clinically significant, record on the medical history CRF.

8.2.3. Clinical Safety Laboratory Assessments

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

8.2.4. Electronic Diary

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

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 oral 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 a secure, restricted 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:

- 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.

- 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. In the event the reaction is ongoing at the end of the study, the reaction will be marked as ongoing.

Investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate participant compliance and safety. These prospectively collected occurrences of local reactions and systemic events are graded as described in Table 1, Table 2, and Table 3.

8.2.4.1. Local Reactions – Reactogenicity

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

Redness and swelling will be measured by the participant and recorded in measuring device units (range: 1 to 21 and >21; an entry in the e-diary of 21 will denote ≥21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 1. 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 1.

If a severe 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/SAE 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 1. 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

Table 1. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
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 case report form and assessed by the investigator using the AE intensity grading scale detailed in Section 10.2.3.

8.2.4.2. Systemic Events

Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), participants will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary that evening. The symptoms will be assessed by the participant according to the grading scale in Table 2.

If a severe 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. Grade 4 reactions will be collected as an AE/SAE 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 2. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness)	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

Table 2. Grading Scale for Systemic Events

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

a. Only an investigator 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 reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

8.2.4.3. Fever Monitoring

A digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) and at any time during the 7 days following vaccination that fever is suspected.

Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary, where possible. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 3 during analysis.

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

If a fever of ≥39.0°C (≥102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor. 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 3. 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 case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of the vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. After vaccination, in the case of a positive confirmed pregnancy, the vaccinated participant may remain in the study for safety and immunogenicity follow-up.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 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 (Section 7).

During the active collection period as described in Section 8.3.1, 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.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each 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 to a minimum of 28 days for AEs and for SAEs, to study completion.

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

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. 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 8.3.1, 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.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. 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 given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities 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.

8.3.5. 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 exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

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

8.3.5.1. 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 exposes a female partner to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to 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 injection, ingestion, inhalation, or skin contact.

    - A male participant, family member, or healthcare provider who has been exposed to the study intervention by injection, ingestion, inhalation, or skin contact then exposes 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, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after study intervention administration.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until

completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion.

- 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.

8.3.5.2. Exposure During Breastfeeding

Exposure during breastfeeding occurs when:

- A vaccinated female participant breastfeeds or donates breast milk to an infant or child at any time during her participation in the study.

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

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure

information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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

8.3.5.3. Occupational Exposure

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.9. Medical Device Deficiencies

Medical devices being provided for use in this study are for the purpose of administering the study intervention. 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 8.3.1 through 8.3.4 and Appendix 2 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

The method of documenting medical device deficiencies is provided in Appendix 5.

8.3.9.2. Follow-Up of Medical Device Deficiencies

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

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

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

8.3.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

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

3. If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.3.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting form as outlined in Sections 8.3.1.1 and 8.3.1.2.

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

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

8.3.10. Medication Errors

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

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of 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.

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE**.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

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

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.2.

8.8. Health Economics

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

8.9. Study Procedures

8.9.1. Visit 1 – 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 administration of the vaccine** are conducted prior to 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.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and evaluate vital signs and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure and record prevaccination temperature.

- Prior to vaccination, perform a urine pregnancy test on WOCBP as described in Section 8.2.5. Record the result in the source documents. A negative pregnancy test result will be required prior to the participant's receiving the study intervention.

- Discuss contraceptive use as described in Section 10.3.4.

- Obtain details of any nonstudy vaccinations as described in Section 6.8.

- Review concomitant medication use as described in Section 6.8.

- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5. If delay criteria are met, reschedule the Visit 1 blood draw and randomization/vaccination for a later date.

- Prior to vaccination, collect a blood sample of approximately 20 mL for antibody assessment.

- 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.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Explain the e-diary technologies available for this study (Section 8.2.3), and assist the participant in downloading the e-diary application onto the participant's own device or, if required, issue a sponsor-provisioned e-diary.

- Work with the participant to set up the device/e-diary and provide training on daily e-diary completion. Ask the participant to complete the reactogenicity e-diary each evening between 6 pm and midnight, starting on Day 1 and completing on Day 7, where Day 1 is the day of vaccination.

- Qualified site staff member(s) will administer a single dose of study intervention into the deltoid muscle of the nondominant arm (preferred arm).

- Observe the participant for any acute reactions for at least 30 minutes after study intervention administration. Record any acute reactions including the time of onset, in the participant's source documents, on the AE page of the CRF, and on the Vaccine SAE Reporting Form if applicable.

- Provide the participant with an ECC and instruct the participant on its use.

- Ask the participant to contact the site staff or investigator immediately if he/she experiences any of the following reactions from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (Section 8.9.3):

  - 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.

    OR

  - Any emergency room attendance or hospitalization.

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

- Advise the participant to inform the study staff of any AEs and SAEs that occur for the duration of the study as described in Section 8.3.

- Request that the participant bring the completed e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and the blinded dispenser/administrator completes the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the daily e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.9.2. Visit 2 – 1-Month Follow-Up (Clinic, 28 to 35 Days After Visit 1)

- Record details of any nonstudy vaccinations and concomitant medications as described in Section 6.8.
- Collect a blood sample of approximately 80 mL for antibody assessment.
- 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. Collect any sponsor-provisioned e-diary.
- Record AEs and SAEs as described in Section 8.3. Obtain and record any missing AE stop dates.
- Complete the source documents.
- The investigator or an authorized designee completes the CRF.

8.9.3. Unscheduled Reactogenicity Visits for a Grade 3 or Suspected Grade 4 Reaction

If a **severe** local reaction (Section 8.2.4.1), **severe** systemic event (Section 8.2.4.2), or fever ≥39.0°C (≥102.1°F) (Section 8.2.4.3) is reported in the 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 an unscheduled visit (Section 8.9.3) 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 body temperature and record any fever (Table 3).
- If present, measure the minimum and maximum diameters of redness at the injection site.
- If present, measure the minimum and maximum diameters of swelling at the injection site.
- Assess any injection site pain in accordance with the reactogenicity grading scale provided in Table 1.
- Assess any systemic events (fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Table 2.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.
- Record AEs and SAEs as described in Section 8.3.1.2.
- Complete the participant's source documents.
- The investigator or an authorized designee will complete the unscheduled-visit-assessment CRF.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to each primary CCI [redacted] objective are described in Section 3.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (Section 9.2). These estimands estimate the vaccine effect in the hypothetical settings where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as MCAR is assumed.

In the primary safety objective evaluations, completely missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

9.1.2. Statistical Hypotheses

This study has 1 primary immunogenicity objective, which is to demonstrate that the immune responses for RSV A and RSV B induced by 3 lots of RSVpreF are equivalent. The objective will be evaluated at 1 month after vaccination for RSV A and RSV B using the evaluable immunogenicity population.

The null hypothesis (H_0) for lot consistency for RSV A and RSV B is as follows:

H_0: $|\ln(\mu_1) - \ln(\mu_2)| \geq \ln(1.5)$ or $|\ln(\mu_1) - \ln(\mu_3)| \geq \ln(1.5)$ or $|\ln(\mu_2) - \ln(\mu_3)| \geq \ln(1.5)$

where ln(1.5) corresponds to a 1.5-fold equivalence margin, and ln(μ1), ln(μ2), and ln(μ3) are the natural log of the geometric mean of RSV antigen-specific NTs from participants receiving RSVpreF in Group 1, Group 2, and Group 3, respectively, measured 1 month after vaccination.

Lot consistency will be declared if the 2-sided 95% CI for the ratio of GMTs for every pair of RSVpreF lots is contained in the interval (0.667, 1.5), for both antigens simultaneously.

9.1.3. Multiplicity Adjustment

No multiplicity adjustment will be applied for this study. The primary objective of equivalence will be achieved only if the 1.5-fold equivalence criterion is met for every pair of between-lot comparisons from 3 lots and for both RSV A and RSV B antigens simultaneously. Each of the 6 statistical tests (3 pairwise comparisons between lots × 2 RSV antigens) will use a 2-sided alpha level of 0.05.

9.2. Analysis Sets

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to study intervention	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All participants who are eligible, receive the study intervention to which they were randomized, have valid and determinate immunogenicity result from the blood sample collected within an appropriate window at 1 month after vaccination, and have no major protocol violations.
mITT	All randomized participants who receive study intervention and have at least 1 valid and determinate assay result after vaccination.
Safety	All randomized participants who receive study intervention.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

Unless stated otherwise, "vaccine group" in this section refers to participants receiving any 1 of the 3 RSVpreF lots or placebo. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

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

The safety analyses will be based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received.

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, and the 95% CIs where applicable.

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

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 Mean Ratios

The GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 vaccine groups and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.3.1.2.2. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results,

calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

CCI

[redacted]

9.3.2. Primary Endpoint(s)

Endpoint	Statistical Analysis Methods
Immunogenicity	GMRs of RSV NTs for each between-lot comparison (Group 1/Group 2, Group 1/Group 3, and Group 2/Group 3) for RSV A and RSV B at 1 month after vaccination will be provided along with associated 2-sided 95% CIs (Section 9.3.1.2.1). Using a 1.5-fold equivalence margin, lot consistency will be declared if the 2-sided 95% CI for each GMR is contained in the interval (0.667, 1.5).

Endpoint	Statistical Analysis Methods
Safety	Descriptive statistics will be provided for each reactogenicity endpoint in the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo. Local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) from Day 1 through Day 7 after vaccination will be presented by severity and cumulatively across severity levels. 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. Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs and SAEs after vaccination will be provided for the pooled RSVpreF lots and placebo. A 3-tier approach will be used to summarize AEs. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between the pooled RSVpreF lots and placebo will be calculated using the test statistic proposed by Miettinen and Nurminen;[22] in addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. There is no preidentified Tier 1 event for this study. A MedDRA preferred term is defined as a Tier 2 event if its incidence is at least 1% in the pooled RSVpreF group or in the placebo group.

9.3.3. Secondary Endpoint(s)

Not applicable.

CCI

[redacted]

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. Only 1 analysis will be performed at the completion of the study.

9.5. Sample Size Determination

Table 4 presents the power to demonstrate that the immune responses induced by 3 lots of RSVpreF are equivalent in regard to the 2 RSV antigens.

Pairwise lot-consistency comparisons will be based on the GMRs and the corresponding 95% CIs. For both antigens, it is assumed that true differences between lots are not larger than 0 (on the natural log scale). The SDs of the log titers for RSV A and RSV B are based on Study C3671001 data.

With 225 evaluable participants per vaccine group and the above assumptions, the power is 93.3% for declaring the overall equivalence of the 3 RSVpreF lots for both RSV A and RSV B.

Allowing for a nonevaluable rate of approximately 10%, up to 1000 participants will be enrolled in the study to provide the required sample size of approximately 900 participants for the evaluable population analysis. Participants who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

Table 4. Power for the Primary Immunogenicity Objective (Lot Consistency)

Endpoint	Within-Lot SD (Log Scale)[a]	Maximum Lot Difference (Log Scale)	Consistency Margin	Number of Evaluable Participants per Vaccine Group	Power to Declare Consistency[b]
RSV A	0.96	0	1.5-fold	225	98.5%
RSV B	1.07	0	1.5-fold	225	94.7%
Overall power to declare consistency for RSV A and RSV B simultaneously					93.3%

a. The reference study is C3671001.
b. The power to declare equivalence between all 3 pairwise comparisons assuming a mean difference of 0 between any 2 RSVpreF lots, at a 0.05 alpha level (2-sided).

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, 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 study 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 his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date 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 ICD(s) during their participation in the study.

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

Participants who are rescreened may be required to sign a new ICD as per IRB, local regulations, etc.

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 his or her 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

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

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.7. 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 clinical study report.

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

Monitoring details describing strategy, 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 retain 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 source data and its origin can be found in the monitoring plan, 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 data) that supports the information entered in the CRF.

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

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the 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.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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 or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (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 investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

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

10.2.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in 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 non-pathogenic, is considered serious.

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding.	All AEs or SAEs associated with exposure during pregnancy or breastfeeding. **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 non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

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

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 his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.
SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

  - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.3.4).

10.3.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.3.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.3.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.3.4. Contraception Methods

Contraceptive use by men or WOCBP should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

   - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;
   - Intravaginal;
   - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;
   - Injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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 TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and TBili for suspected 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 TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities**.

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

10.5. Appendix 5: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

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

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

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

10.5.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 2 (Section 10.2.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.5.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 2 (Section 10.2.2).
SADE Definition
• An SADE is defined as an adverse device effect 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 is a serious adverse device effect 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 and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 2 (Section 10.2.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 2, Section 10.2.

10.5.5. Reporting of SAEs

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

10.5.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, a SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.6. Appendix 6: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures is expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

10.6.1. 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 participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Obtain details of any nonstudy vaccinations, concomitant medications, and treatments as described in Section 6.8.
- Confirm that the participant is adhering to the contraception method(s) required in the protocol.

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

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
dLIA	direct-binding Luminex immunoassay
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FIH	first-in-human
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMT	geometric mean titer

Abbreviation	Term
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
CCI	[redacted]
IM	intramuscular
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous
IWR	interactive Web-based response
LAIV	live attenuated influenza vaccine
LFT	liver function test
LMIC	low- and middle-income country
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
MCAR	missing completely at random
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
msLRTI	moderate to severe lower respiratory tract illness
N/A	not applicable
NT	neutralizing titer
PCR	polymerase chain reaction
PFS	prefilled syringe
PPE	personal protective equipment
PT	prothrombin time
QTL	quality tolerance limit
CCI	[redacted]
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

Abbreviation	Term
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
Tdap	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
Th2	T-helper type 2
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
WOCBP	woman/women of childbearing potential

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