A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING, FIRST-IN-HUMAN STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE IN HEALTHY ADULTS

Investigational Product Number:	PF-06928316
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Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 2	11 Jun 2019	[redacted] • Updated inclusion criteria for expanded-cohort subjects for revaccination. • Added study procedures for each visit in the revaccination stage (Visit 7 to Visit 11). • Updated Section 9 to reflect addition of the revaccination stage to the study design. [redacted]
Protocol Amendment 1	05 Jun 2018	Schedule of Activities (footnote b) and Sections 3 and 6.2: Added text to describe ≥4-hour observation of the first 4 subjects in the 18- to 49-year-old age group vaccinated at the first site only, as requested by the central institutional review board (IRB).

		Section 3: Revised text to clarify the randomization process in the sentinel and expanded cohorts. Section 4.2: For safety reasons, expanded the exclusion criteria to include history of severe allergic reaction to natural rubber latex (all cohorts) and history of severe allergic reaction to any substance (expanded cohort only). Sections 4.2, 5.8.2, and 5.8.3: To address inconsistency with Section 4.3, added inhaled/nebulized corticosteroids to the list of permitted corticosteroids. Section 5.1.2: Clarified that the personnel not directly involved in the study will review "safety data" (ie, rather than "unblinded data") according to an internal review committee (IRC) charter. Section 5.4: Deleted the Subject Compliance section because it is a duplicate of Section 5.3. Sections 6.1 and 6.10: Added text to address the exception granted to Vaccines by the Global Standards Board to collect subjects' full date of birth. Section 6.17.3: Deleted the third bullet point (about obtaining details of the date of

		resolution of any respiratory symptoms) because it is a duplicate of the fourth bullet point. Section 7.6: Clarified that meeting a stopping rule will halt "randomization" (rather than "enrollment"). Section 9.5: Clarified that review by the IRC will determine if "randomization" (rather than "enrollment") in the next higher dose level should begin. Appendix 2: Added the appendix to provide criteria for South Africa only, because of country-specific requirements. Throughout: Made minor editorial revisions as appropriate.
Original protocol	29 November 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Indication

The respiratory syncytial virus stabilized prefusion F subunit vaccine (RSV vaccine) is being developed for 2 indications:

- **Maternal:** Prevention of respiratory syncytial virus (RSV)-associated lower respiratory tract disease in infants by active immunization of pregnant women.
- **Older adult:** Prevention of RSV-associated moderate to severe lower respiratory tract disease in adults 60 years of age and older via active immunization.

Primary Objective:	Primary Endpoints:
To describe the safety and tolerability of an RSV vaccine given alone or concomitantly with seasonal inactivated influenza vaccine (SIIV).	**Sentinel and expanded cohorts:** • Local reactions within 14 days after Vaccination 1. • Systemic events within 14 days after Vaccination 1. • Adverse events (AEs) within 1 month after Vaccination 1. • Medically attended AEs and serious adverse events (SAEs) through 12 months after Vaccination 1. **Expanded cohort:** • AEs within 1 month after Vaccination 2.

Study Design

This is a Phase 1/2 randomized, placebo-controlled, observer-blind, dose-finding first-in-human (FIH) study.

The study will describe the safety, tolerability, and immunogenicity of up to 6 different RSV vaccine candidates [redacted] at 3 escalating dose levels of 60 µg [redacted] 120 µg [redacted] and 240 µg [redacted] of the prefusion RSV F antigen, with or without aluminum hydroxide ($Al[OH]_3$) when administered alone or concomitantly with SIIV.

This study will utilize a sentinel cohort (Phase 1) and an expanded cohort (Phase 2). The age groups will run in parallel.

In the sentinel cohort (Phase 1), subjects will be enrolled into 2 age groups:

- Male and female subjects 18 to 49 years of age.
- Male and female subjects 50 to 85 years of age.

In the expanded cohort (Phase 2), subjects will be enrolled into 2 age groups:

- Male and female subjects 18 to 49 years of age.
- Male and female subjects 65 to 85 years of age.

A single dose of RSV vaccine will be given to sentinel-cohort subjects to assess 3 escalating dose levels of the RSV vaccine candidate with or without $Al(OH)_3$. The first 4 subjects vaccinated at the first site will be in the 18- to 49-year-old age group. These subjects must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions. Vaccination of the remaining subjects in both age groups will commence no sooner than 48 hours after the fourth subject received his or her vaccination.

The expanded cohort will assess the concomitant use of SIIV when given to subjects receiving 1 of 3 dose levels of the RSV vaccine candidate with or without $Al(OH)_3$.

Subsequently, at approximately 12 months after Visit 1, selected subjects in the expanded cohort will be invited to participate in the revaccination stage. Subjects in the 240-μg dose group who received an initial dose of the RSV vaccine with or without $Al(OH)_3$ will be revaccinated with the same dose and formulation of the RSV vaccine alone or concomitantly with SIIV. The SIIV or placebo assignment and the vaccination scheme will be the same as for the first year of the study. As a control, the placebo group will also be revaccinated with placebo alone and then followed by SIIV alone. Subjects will receive 2 intramuscular injections at Visit 7 and 1 intramuscular injection at Visit 8. The safety, tolerability, and immunogenicity of the second dose will be evaluated.

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all pertinent aspects of the study.

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

   Note: Healthy subjects with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

3. Willing and able to comply with scheduled visits, vaccination plan, laboratory tests, and other study procedures.

4. Male subject who is able to father children and willing to use a highly effective method of contraception as outlined in this protocol until at least 28 days after the last dose of investigational product; female subject who is of childbearing potential and at risk for pregnancy and who is willing to use a highly effective method of contraception as outlined in this protocol until at least 28 days after the last dose of investigational product; male subject not able to father children; female subject not of childbearing potential.

5. **Sentinel-cohort subjects only:** Male and female adults 18 to 85 years of age at the time of enrollment (signing of the ICD).

6. **Expanded-cohort subjects only:** Male and female adults 18 to 49 years of age or 65 to 85 years at the time of enrollment (signing of the ICD).

7. **Expanded-cohort subjects for revaccination only:** Subjects in the 240-µg dose group and the placebo group who completed primary vaccinations at Visit 1 and Visit 2 and signed and dated the ICD for participating in the revaccination stage.

Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. **Sentinel-cohort subjects only:** Any screening hematology and/or blood chemistry laboratory value listed in Table 7 that meets the definition of a ≥ Grade 1 abnormality.

   Note: With the exception of bilirubin, subjects with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same subject).

2. **Sentinel-cohort subjects only:** Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

3. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4. Participation in other studies involving investigational product within 28 days prior to study entry and/or during study participation.

5. Known infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

6. Previous vaccination with any licensed or investigational RSV vaccine before enrollment into the study, or planned receipt throughout the study of nonstudy RSV vaccine.

7. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product(s), including natural rubber latex. In addition, for expanded-cohort subjects only, history of severe allergic reaction (eg, anaphylaxis) to any substance.

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

9. Subjects who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

10. Subject with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, temporal arteritis, psoriasis, and insulin-dependent diabetes mellitus.

11. Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration or planned receipt throughout the study.

12. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

14. Women who are pregnant or breastfeeding.

15. **Expanded-cohort subjects only (including subjects for revaccination):** Vaccination with any influenza vaccine within 6 months (182 days) before investigational product administration.

16. **Expanded-cohort subjects only (including subjects for revaccination):** Allergy to egg proteins (egg or egg products) or chicken proteins.

Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

CCI [redacted]

There are 3 different presentations of RSV vaccine drug product representing 3 different dose levels of RSV antigen (60 μg, 120 μg, and 240 μg). The vaccine product lyophilized cake is reconstituted by diluent with either sterile water for injection or a sterile suspension of $Al(OH)_3$ in water for injection.

Seasonal Inactivated Influenza Vaccine (expanded cohort only)

Commercially available quadrivalent SIIV will be used for subjects 18 to 49 years of age.

Commercially available high-dose trivalent SIIV (if available) or quadrivalent SIIV will be used for subjects 65 to 85 years of age.

Placebo

The placebo for RSV vaccine will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

The placebo for SIIV (expanded cohort) will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

Statistical Methods

The study sample sizes are not based on statistical considerations. Statistical analysis will be descriptive in nature.

All safety and tolerability endpoints will be summarized as the proportion of subjects with events. Additionally, exact 2-sided 95% confidence intervals for proportions will be provided as applicable.

For immunogenicity endpoints, geometric mean titer (GMT) and geometric mean fold rise (GMFR) from baseline will be calculated by vaccine group along with the 95% confidence intervals. The ratios of postvaccination GMT between vaccine sequences in the expanded cohort with associated 2-sided 95% confidence interval will also be constructed as appropriate.

All of the safety, tolerability, and immunogenicity data will be summarized for the sentinel cohort and expanded cohort separately for each age group. In addition, sentinel and expanded cohorts will be combined and analyzed together by vaccine group as appropriate.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Sentinel Cohort

Visit Number	0	1	2	3	4	5	6	7
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**2-Month Follow-up Visit**	**3-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**
Visit Window (Days)	**2 to 14 Days Before Visit 1**	**Day 1**	**14 to 18 Days After Visit 1**	**28 to 35 Days After Visit 1**	**56 to 70 Days After Visit 1**	**84 to 105 Days After Visit 1**	**168 to 210 Days After Visit 1**	**350 to 378 Days After Visit 1**
Obtain informed consent	X							
Assign subject number	X							
Obtain demography and medical history data	X							
Assess tobacco usage	X							
Obtain details of medications currently taken	X							
Perform physical examination	X							
Measure vital signs	X							
Collect blood sample for hematology and chemistry laboratory tests[a]	~10 mL		~10 mL					
Collect blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL							
Perform urine pregnancy test (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X	X	X	X	
Confirm eligibility	X	X						
Review hematology and chemistry results		X		X				
Measure temperature (oral)	X	X						

Visit Number	0	1	2	3	4	5	6	7
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**2-Month Follow-up Visit**	**3-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**
Visit Window (Days)	**2 to 14 Days Before Visit 1**	**Day 1**	**14 to 18 Days After Visit 1**	**28 to 35 Days After Visit 1**	**56 to 70 Days After Visit 1**	**84 to 105 Days After Visit 1**	**168 to 210 Days After Visit 1**	**350 to 378 Days After Visit 1**
Review temporary delay criteria		X						
Confirm use of appropriate contraceptives (if appropriate)	X	X	X	X				
Assign randomization number		X						
Collect blood sample for antibody assessment		~100 mL	~50 mL	~100 mL	~50 mL	~50 mL	~50 mL	~50 mL
Administer investigational product		X						
Assess acute reactions for at least 30 minutes after investigational product administration[b]		X						
Provide subject with 14-day e-diary, thermometer, and measuring device		X						
Review e-diary data (daily review is optimal during the active diary period)		X						
Review and collect e-diary			X					
Collect AEs, medically attended AEs, and SAEs as appropriate	X	X	X	X	X	X	X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus.

a. Screening tests: Hematology - hemoglobin, complete blood count with differential, and platelets. Blood chemistry - alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.

b. At the first site only, the first 4 subjects in the 18- to 49-year-old age group will be observed at the site for at least 4 hours after investigational product administration. Further vaccination in both age groups will commence no sooner than 48 hours after the fourth subject received his or her vaccination.

Expanded Cohort

Visit 1 to Visit 6 will be performed for all subjects in the expanded cohort. The unplanned respiratory illness visit and the unplanned respiratory convalescent visit are required only for respiratory illness occurring between 15 days after Vaccination 1 and Visit 5.

Visit Number	1	2	3	4	5	6		
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Month Follow-up Visit**	**3-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**Unplanned Respiratory Illness Visit**	**Unplanned Respiratory Convalescent Visit**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 1**	**56 to 70 Days After Visit 1**	**84 to 105 Days After Visit 1**	**168 to 210 Days After Visit 1**	**350 to 378 Days After Visit 1**	**Within 7 Days After Respiratory Illness Onset[a]**	**28 to 35 Days After Respiratory Illness Visit[b]**
Obtain informed consent	X							
Assign subject number	X							
Obtain demography and medical history data	X							
Assess tobacco usage	X							
Perform physical examination	X							
Perform urine pregnancy test for female subjects (if appropriate)	X	X						
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X
Confirm inclusion and exclusion criteria	X							
Obtain prevaccination temperature (oral)	X	X						
Review temporary delay criteria	X	X						
Confirm use of appropriate contraceptives (if appropriate)	X	X	X					
Assign randomization number	X							
Obtain midturbinate nasal swab (collected by site staff)	X						X	X

Visit Number	1	2	3	4	5	6		
Visit Description	**Vaccination 1**	**Vaccination 2**	**2-Month Follow-up Visit**	**3-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**Unplanned Respiratory Illness Visit**	**Unplanned Respiratory Convalescent Visit**
Visit Window (Days)	**Day 1**	**28 to 35 Days After Visit 1**	**56 to 70 Days After Visit 1**	**84 to 105 Days After Visit 1**	**168 to 210 Days After Visit 1**	**350 to 378 Days After Visit 1**	**Within 7 Days After Respiratory Illness Onset[a]**	**28 to 35 Days After Respiratory Illness Visit[b]**
Obtain sample for antibody assessment (~50 mL per blood sample)	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL	~50 mL
Administer investigational product	X	X						
Assess acute reactions for at least 30 minutes after investigational product administration	X	X						
Provide subject with 14-day e-diary, thermometer, and measuring device	X							
Review e-diary data (daily review is optimal during the active diary period)	X							
Obtain midturbinate nasal swab(s) (self-collected by subject)[c]	----------X----------							
Review and/or collect e-diary		X						
Collect AEs, medically attended AEs, and SAEs as appropriate	X	X	X	X	X	X	X	X
Surveillance reminder contact	Starting on Day 15 after Vaccination 1, contact the subject approximately every week until Visit 5							

Abbreviation: e-diary = electronic diary.

a. Starting on Day 15 after Vaccination 1, subjects will be seen in the clinic or at home, ideally within 7 days after the onset of a respiratory illness.
b. Visit may be performed in the clinic or in the subject's home.
c. Starting on Day 15 after Vaccination 1 until Visit 5, subjects will be asked to collect midturbinate swab(s) at the onset of a respiratory illness.

Expanded-Cohort Subjects for Revaccination

Visit 7 to Visit 11 are applicable only to subjects of the 240-µg dose groups and the placebo group in the expanded cohort.

Visit Number	7	8	9	10	11
Visit Description	**Vaccination 3**	**Vaccination 4**	**2-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**
Visit Window (Days)	**350 to 420 Days After Visit 1[a]**	**28 to 35 Days After Visit 7**	**56 to 70 Days After Visit 7**	**168 to 210 Days After Visit 7**	**350 to 378 Days After Visit 7**
Obtain informed consent	X				
Perform physical examination	X				
Perform urine pregnancy test for female subjects (if appropriate)	X	X			
Collect nonstudy vaccine information	X	X	X	X	X
Review inclusion and exclusion criteria	X				
Obtain prevaccination temperature (oral)	X	X			
Review temporary delay criteria	X	X			
Confirm use of appropriate contraceptives (if appropriate)	X	X	X		

Visit Number	7	8	9	10	11
Visit Description	**Vaccination 3**	**Vaccination 4**	**2-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**
Visit Window (Days)	**350 to 420 Days After Visit 1[a]**	**28 to 35 Days After Visit 7**	**56 to 70 Days After Visit 7**	**168 to 210 Days After Visit 7**	**350 to 378 Days After Visit 7**
Obtain sample for antibody assessment (~50 mL per blood sample)	~50 mL[b]	~50 mL	~50 mL	~50 mL	~50 mL
Administer investigational product	X	X			
Assess acute reactions for at least 30 minutes after investigational product administration	X	X			
Provide subject with 14-day e-diary, thermometer, and measuring device	X				
Review e-diary data (daily review is optimal during the active diary period)	X				
Review and/or collect e-diary		X			
Collect AEs, medically attended AEs, and SAEs as appropriate	X	X	X	X	X

Abbreviation: e-diary = electronic diary.

a. Visit 6 and Visit 7 can be conducted on the same day.
b. A blood sample will be collected at Visit 7 **only** if Visit 6 and Visit 7 are not conducted on the same day.

1. INTRODUCTION

1.1. Indication

The RSV stabilized prefusion F subunit vaccine (RSV vaccine) is being developed for 2 indications:

- **Maternal:** Prevention of respiratory syncytial virus (RSV)-associated lower respiratory tract disease in infants by active immunization of pregnant women.

- **Older Adult:** Prevention of RSV-associated moderate to severe lower respiratory tract disease in adults 60 years of age and older via active immunization.

1.2. Background and Rationale

Human respiratory syncytial virus (HRSV) is the type species of the genus *Pneumovirus*, subfamily Pneumovirinae, family Paramyxoviridae, order Mononegavirales. Human respiratory syncytial virus (HRSV) exists as 2 antigenic subgroups, A and B, which exhibit genomewide sequence divergence. RSV is a global pathogen, causing yearly wintertime epidemics in temperate climates, usually between late fall and early spring, lasting 3 to 4 months in a community. In tropical climates, there is no distinct seasonality and outbreaks are more unpredictable, continuous, and generally associated with rainy seasons.[1]

Since its identification in 1956, RSV has consistently been noted as the single most important cause of lower respiratory tract infection (LRTI) in infants <1 year of age worldwide. RSV is most notably associated with signs and symptoms of increased airway resistance manifested as wheezing and, in the young child, diagnosed as bronchiolitis. The acute illness usually lasts about 5 to 10 days, but the cough may be prolonged for several weeks.[1] Globally, the incidence of RSV-associated acute LRTI was estimated in 2015 to be approximately 33 million episodes, which resulted in about 3.2 million hospital admissions and about 59,600 hospital deaths in children younger than 5 years. In children younger than 6 months, it is estimated that globally approximately 1.4 million hospital admissions, and approximately 27,300 hospital deaths, were due to RSV-associated acute lower respiratory infection.[2] In addition to infants and young children, RSV is increasingly recognized as an important cause of severe respiratory disease in adults 60 years of age or older as well as individuals with underlying cardiopulmonary and immunocompromised conditions.[1] The clinical presentation of RSV in older adults is not distinctive, and more severe illness is often diagnosed as exacerbation of comorbid conditions, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure.[1] It is estimated that between 11,000 and 17,000 adults die of RSV infection annually in the United States, with approximately 10-fold more admitted to hospital with respiratory symptoms.[3] In a US study, it was estimated that the yearly rate of RSV hospitalization among persons 50 to 64 years old was 0.82/1000, and among persons ≥65 years of age it was 2.5/1000.[4]

Currently, there is no vaccine to protect against RSV disease. Treatment consists primarily of supportive care. There is, however, a prophylactic humanized monoclonal antibody against the RSV fusion (F) glycoprotein, palivizumab (Synagis, AstraZeneca), with demonstrated safety and efficacy against severe RSV disease in young infants. The antibody is costly, requires multiple monthly injections, and is recommended for use only in high-risk and premature infants.[5,6] The protective effect of Synagis is definitive proof of concept that serum-neutralizing antibody directed against the F protein can provide clinically meaningful protection against RSV lower respiratory tract disease in young infants.

Pfizer is developing a vaccine 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.

The aim of maternal immunization is to increase maternal neutralizing antibodies transferred by the placenta to newborns such that the infant's RSV serum neutralization titers will remain above a protective threshold through the period of greatest neonatal risk, including the time of greatest immunologic and pulmonary immaturity. Maternal immunization is an increasingly accepted strategy, given the efficacy and safety of aluminum-containing tetanus, diphtheria, and acellular pertussis vaccine (TdaP) in pregnancy for mother and baby, the very good safety record of maternal immunization against influenza during annual seasonal (nonpandemic) vaccinations and during the 2009 pandemic, and the increasing evidence of infant benefit from maternal influenza immunization.[7,8,9,10,11]

Maternal immunization to protect infants is anticipated to overcome the barriers to direct infant immunization. One such barrier is the very early peak of RSV disease (approximately 2 months after birth),[12] which leaves little time to elicit a protective immune response. Other barriers include the immaturity of the neonatal immune system and potential suppression of active RSV antibody responses by maternal antibody.[13] Perhaps the greatest barrier to direct infant immunization is the history of vaccine-mediated RSV disease enhancement following immunization of RSV-naive infants with a formalin-inactivated RSV vaccine (FI-RSV).[14] 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.[15] Fortunately, disease enhancement has never been observed in RSV-experienced individuals after immunization with any RSV vaccine candidate.[16] Pregnant women are universally RSV-experienced, so that they are not at risk for a disease-enhancing immune response to the vaccine that could exacerbate infection in themselves or their infants. A previous study of maternal immunization with an investigational RSV vaccine has shown an acceptable safety profile with a postfusion RSV F antigen that elicited a relatively weak RSV-neutralizing antibody response but a higher nonneutralizing RSV-binding antibody response in pregnant women.[17] In a standard cotton rat model, the Pfizer vaccine candidate shows no sign of causing disease enhancement.

The maternal immunization approach is supported by the correlations of naturally acquired maternal and cord blood RSV-neutralizing antibody titers with the duration of passive infant protection from RSV and reduction in infant hospitalization due to RSV disease.[18,19,20]

The aim of RSV immunization in adults 60 years of age and over is to boost the immune response sufficiently to protect against RSV disease before each RSV season. After RSV natural infection, there is only a relatively short duration of immunity.[1] In 3 independent natural history studies, RSV-infected older adults had significantly lower serum RSV-neutralizing antibody titers and RSV-specific immunoglobulin G (IgG) levels than uninfected age-matched controls.[3,21] Additional immune mechanisms may also aid in protection, but the existing evidence supports an important role for serum neutralizing antibody titers in reducing the risk of RSV disease in older adults.

CCI [redacted] 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.

Pfizer preclinical evaluation in mice and cotton rats has demonstrated that a stabilized prefusion F vaccine elicits robust RSV A– and RSV B–neutralizing antibody responses. In contrast to RSV-naive rodents, adult humans are universally seropositive with a range of naturally elicited antibody titers. Pfizer preclinical studies in cotton rats and nonhuman primates (NHPs; rhesus macaques) demonstrated improved immunogenicity with aluminum hydroxide ($Al[OH]_3$)-containing formulations. The inclusion of $Al(OH)_3$ enhanced protection in the upper airways of challenged cotton rats.

This Phase 1/2, randomized, placebo-controlled, observer-blinded dose-finding study will be the first-in-human (FIH) evaluation of the investigational RSV CCI vaccine in healthy adults 18 to 85 years of age. This study will evaluate the safety, tolerability, and immunogenicity of up to 6 CCI formulations CCI at 3 escalating doses of 60 µg CC [redacted] 120 µg CC [redacted] and 240 µg CCI [redacted] of the prefusion RSV F antigen with or without $Al(OH)_3$, when administered alone or concomitantly with seasonal inactivated influenza vaccine (SIIV) to select the optimal dose levels and formulations to support both the maternal and older adult indications.

It is anticipated that an RSV vaccine may frequently be given with a seasonal influenza vaccine. Therefore, this study will also assess any impact on immune responses to either vaccine when the RSV and seasonal influenza vaccines are given concomitantly.

In addition, subjects will be asked to attend additional visits if they experience a respiratory infection following the first vaccination. The purpose of the illness visits is to describe the relationship between serological parameters and a confirmed RSV infection and/or RSV-associated disease symptoms and to develop viral detection assays and procedures for case capture for future efficacy studies.

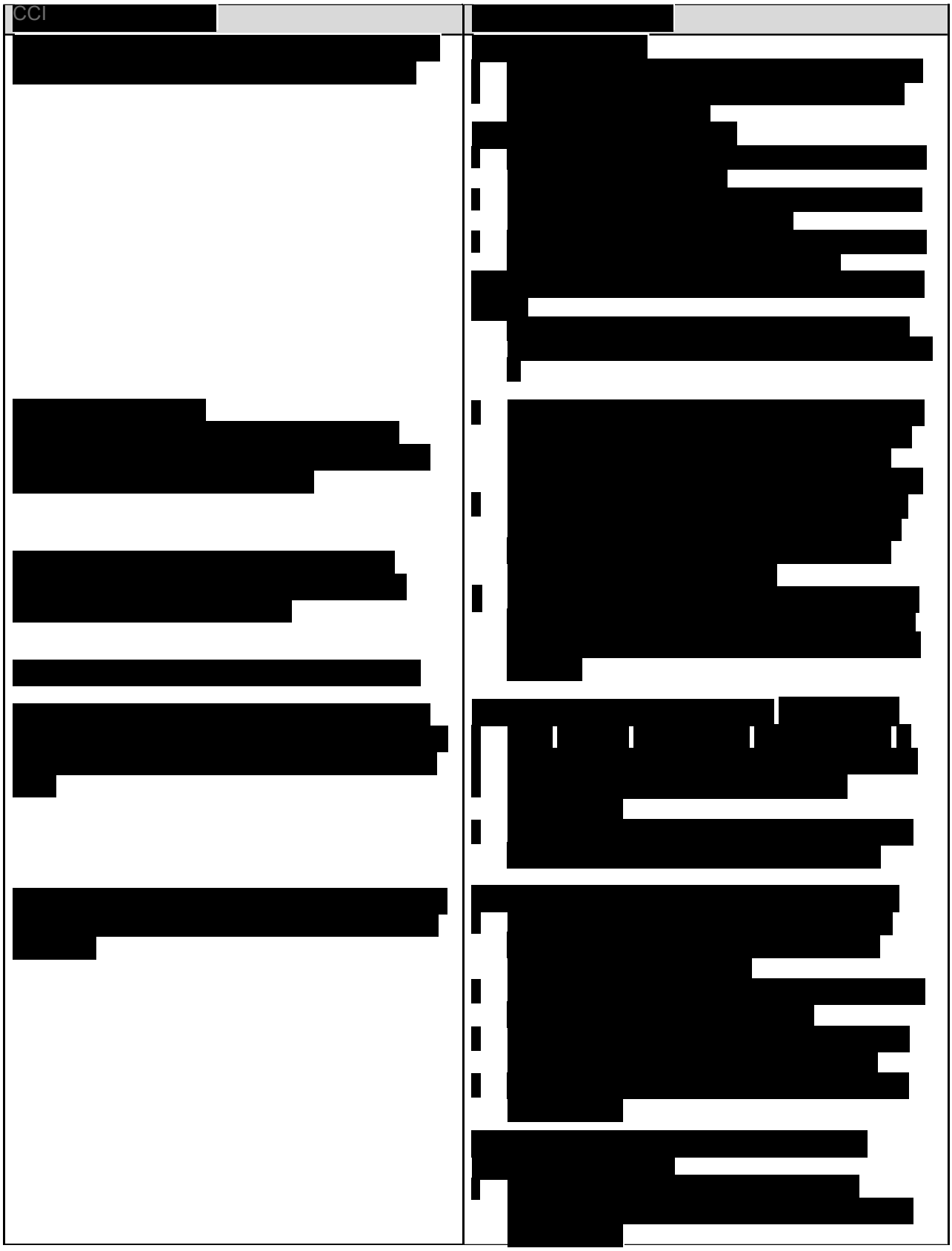
Interim data 1 month after initial vaccination of the 3 dose levels of RSV vaccine, with or without $Al(OH)_3$, administered to subjects of both age groups in the sentinel cohort and subjects of the 18- to 49-year age group in the expanded cohort have shown the vaccine to be immunogenic and well tolerated. There was a trend toward greater immunogenicity at the 240-µg dose level.

To assess if a second vaccine dose elicits similar or higher antibody responses than the first vaccine dose, subjects who received an initial 240-µg dose with or without $Al(OH)_3$ will be revaccinated with the same dose and formulation 12 months later. Revaccination with the highest dose will maximize the chances of observing a high immune response. The 240-µg RSV vaccine formulations will be given alone or concomitantly with SIIV, as at the initial vaccination. As a control, the placebo group will also be revaccinated with placebo alone and then followed by SIIV alone. The safety, tolerability, and immunogenicity of the second dose will be evaluated.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure. The SRSD for the SIIV will be the product information for the country where the vaccine was procured.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoints:**
To describe the safety and tolerability of an RSV vaccine given alone or concomitantly with SIIV.	**Sentinel and expanded cohorts:** • Local reactions within 14 days after Vaccination 1. • Systemic events within 14 days after Vaccination 1. • Adverse events (AEs) within 1 month after Vaccination 1. • Medically attended AEs and serious adverse events (SAEs) through 12 months after Vaccination 1. **Expanded cohort:** • AEs within 1 month after Vaccination 2.
Secondary Objectives:	**Secondary Endpoints:**
Sentinel and expanded cohorts: To describe the immune responses elicited by an RSV vaccine alone (sentinel and expanded cohorts) or with SIIV (expanded cohort only). **Expanded cohort:** To describe the immune responses elicited by SIIV alone or with an RSV vaccine.	**Sentinel cohort:** • RSV A– and RSV B–neutralizing antibody titers measured before Vaccination 1, and 2 weeks and 1, 2, 3, and 6 months after Vaccination 1. **Expanded cohort:** • RSV A– and RSV B–neutralizing antibody titers measured before Vaccination 1, and 1, 2, 3, and 6 months after Vaccination 1. **Expanded cohort:** • Hemagglutination inhibition assay (HAI) titers for all strains in the SIIV measured before and 1 month after SIIV administration.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3. STUDY DESIGN

This is a Phase 1/2 randomized, placebo-controlled, observer-blind, dose-finding FIH study.

The study will evaluate the safety, tolerability, and immunogenicity of up to 6 different RSV vaccine candidates [redacted] at 3 escalating dose levels of 60 µg [redacted] 120 µg [redacted] and 240 µg [redacted] of the prefusion RSV F antigen, with or without $Al(OH)_3$, when administered alone or concomitantly with SIIV.

This study will utilize a sentinel cohort (Phase 1) and an expanded cohort (Phase 2) for each dose level in each age group (see Figure 1**)**. The age groups will run in parallel but independently from each other.

In the sentinel cohort (Phase 1), subjects will be enrolled into 2 age groups:

- Male and female subjects 18 to 49 years of age.
- Male and female subjects 50 to 85 years of age.

In the expanded cohort (Phase 2), subjects will be enrolled into 2 age groups:

- Male and female subjects 18 to 49 years of age.
- Male and female subjects 65 to 85 years of age.

A single dose of RSV vaccine will be given to sentinel-cohort subjects to assess 3 escalating dose levels of the RSV vaccine candidate with or without $Al(OH)_3$. The first 4 subjects vaccinated at the first site will be in the 18- to 49-year-old age group. These subjects must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions. Vaccination of the remaining subjects in both age groups will commence no sooner than 48 hours after the fourth subject received his or her vaccination.

The expanded-cohort data will be used to assess the concomitant use of SIIV when given to subjects receiving 1 of 3 dose levels of the RSV vaccine candidate with or without $Al(OH)_3$.

In the expanded cohort, the relationship between serological parameters and a confirmed RSV infection and/or RSV-associated disease symptoms will be assessed and samples will be used to develop viral detection assays for future efficacy studies.

An internal review committee (IRC) and an external data monitoring committee (E-DMC) will monitor safety in this study (refer to Section 9.5).

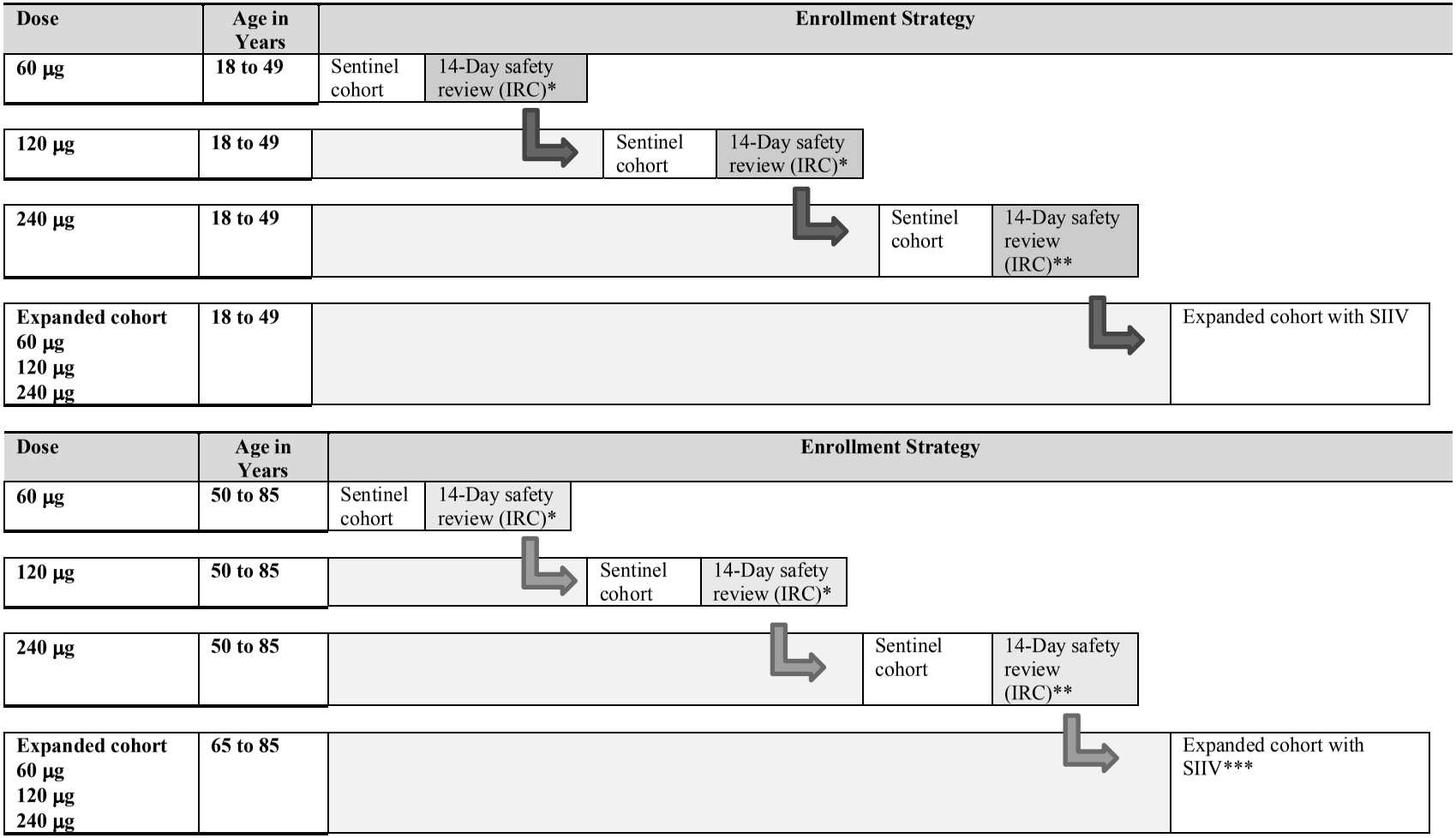
In the sentinel cohort, subjects will receive a single intramuscular dose of the RSV vaccine candidate with or without $Al(OH)_3$ or placebo. Central randomization will take place in a 3:3:1 ratio for each dose level by age strata (See Table 1). Eligible subjects will be randomly assigned to the sentinel group, starting at the 60-µg dose level. For each age group,

randomization into sentinel groups at the 120-µg dose level will progress only if the 14-day safety and tolerability data reviewed by the IRC are deemed acceptable. For each age group, randomization progression to the 240-µg dose level will take place only if the 14-day safety and tolerability data from the 120-µg dose level are deemed acceptable by the IRC. For each age group, the IRC will recommend proceeding with randomization of subjects in the expanded cohort at dose levels where the safety data were deemed acceptable by the IRC (see Figure 1). One-month immunogenicity data from the sentinel group(s) may be used to determine if a dose level(s) can be discontinued from the expanded cohort. Stopping rules for randomization during the study are defined in Section 7.6.

In the expanded cohort, subjects will be randomized equally across each dose level within each age group (see Table 2) via center-based randomization. Subjects in the expanded cohort will receive 2 intramuscular injections at Visit 1 and 1 intramuscular injection at Visit 2. Subjects in the expanded cohort will be asked to attend additional visits if they experience respiratory illness symptoms that last longer than 24 hours during the interval from Day 15 after Vaccination 1 until Visit 5.

Subsequently, at approximately 12 months after Visit 1, selected subjects in the expanded cohort will be invited to participate in the revaccination stage. Subjects in the 240-µg dose group who received an initial dose of the RSV vaccine with or without $Al(OH)_3$ will be revaccinated with the same dose and formulation of the RSV vaccine alone or concomitantly with SIIV. The SIIV or placebo assignment and the vaccination scheme will be the same as for the first year of the study. As a control, the placebo group will also be revaccinated with placebo alone and then followed by SIIV alone. Subjects will receive 2 intramuscular injections at Visit 7 and 1 intramuscular injection at Visit 8. The safety, tolerability, and immunogenicity of the second dose will be evaluated.

Figure 1. Enrollment Strategy for Subjects



*14-Day safety review by internal review committee (IRC). If the safety data in the sentinel cohort in a given age group are acceptable, the IRC will recommend proceeding with randomization of the sentinel cohort at the next dose level for the specified age group.

**14-Day safety review by internal review committee (IRC). If the safety data in the sentinel cohort 240-µg dose level are acceptable, the IRC will recommend proceeding with randomization of additional subjects to the expanded cohort at all 3 dose levels.

***Commercially available seasonal inactivated influenza vaccine (SIIV) or SIIV high-dose (HD) will be used for subjects 65 to 85 years of age. Study sites will be provided with details of which commercially available SIIV or SIIV HD will be provided prior to the start of enrollment of the expanded cohort.

3.1. Number of Subjects

In total, up to approximately 1182 subjects will be randomized if all dose levels are administered to the expanded cohort. Up to approximately 168 healthy subjects will be randomized in the sentinel cohort and up to approximately 1014 healthy subjects will be randomized in the expanded cohort (see Table 1 and Table 2 below). In addition, approximately 390 subjects in the expanded cohort will be invited to participate in the revaccination stage of the study (see Table 3).

An allocation target will not be set by sex; however, the intention is for sites to enroll at least 50% women within each dose level group in the sentinel and expanded cohorts of the 18- to 49-year age group. If there is a predominance of one sex enrolled, the sponsor may give direction to sites about sex-based enrollment.

Subjects who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

Table 1. Sentinel Cohort

Dose/Formulation/Sequence		Males and Females 18 to 49 Years of Age	Males and Females 50 to 85 Years of Age	Total
	Visit 1			
60 µg	RSV	12	12	24
	RSV+$Al(OH)_3$	12	12	24
	Placebo	4	4	8
	Total	**28**	**28**	**56**
120 µg	RSV	12	12	24
	RSV+$Al(OH)_3$	12	12	24
	Placebo	4	4	8
	Total	**28**	**28**	**56**
240 µg	RSV	12	12	24
	RSV+$Al(OH)_3$	12	12	24
	Placebo	4	4	8
	Total	**28**	**28**	**56**
Total sentinel		**84**	**84**	**168**

Abbreviations: $Al(OH)_3$ = aluminum hydroxide; RSV = respiratory syncytial virus vaccine.

Table 2. Expanded Cohort

Dose/Formulation/Sequence			Males and Females 18 to 49 Years of Age	Males and Females 65 to 85 Years of Age	Total
	Visit 1	Visit 2			
60 µg	RSV SIIV	Placebo	39	39	78
	RSV Placebo	SIIV	39	39	78
	RSV+$Al(OH)_3$ SIIV	Placebo	39	39	78
	RSV+$Al(OH)_3$ Placebo	SIIV	39	39	78
120 µg	RSV SIIV	Placebo	39	39	78
	RSV Placebo	SIIV	39	39	78
	RSV+$Al(OH)_3$ SIIV	Placebo	39	39	78
	RSV+$Al(OH)_3$ Placebo	SIIV	39	39	78
240 µg	RSV SIIV	Placebo	39	39	78
	RSV Placebo	SIIV	39	39	78
	RSV+$Al(OH)_3$ SIIV	Placebo	39	39	78
	RSV+$Al(OH)_3$ Placebo	SIIV	39	39	78
	Placebo Placebo	SIIV	39	39	78
	Total expanded		**507**	**507**	**1014**
	Total study size Sentinel + expanded		**591**	**591**	**1182**

Abbreviations: $Al(OH)_3$ = aluminum hydroxide; RSV = respiratory syncytial virus vaccine; SIIV = seasonal inactivated influenza vaccine.

Table 3. Expanded-Cohort Subjects for Revaccination

Dose/Formulation/Sequence			Males and Females 18 to 49 Years of Age	Males and Females 65 to 85 Years of Age	Total
	Visit 7	**Visit 8**			
240 µg	RSV SIIV	Placebo	39	39	78
	RSV Placebo	SIIV	39	39	78
	RSV+$Al(OH)_3$ SIIV	Placebo	39	39	78
	RSV+$Al(OH)_3$ Placebo	SIIV	39	39	78
Placebo	Placebo Placebo	SIIV	39	39	78
		Total subjects	195	195	390

Abbreviations: $Al(OH)_3$ = aluminum hydroxide; RSV = respiratory syncytial virus vaccine; SIIV = seasonal inactivated influenza vaccine.

3.2. Duration of Subject Participation

Each subject will participate in the study for approximately 12 months except the expanded-cohort subjects for revaccination, who will participate in the study for approximately 24 months.

3.3. Duration of Study

The approximate duration of each stage is anticipated to be as follows.

Sentinel Cohort: Assuming a 5-month enrollment period, this phase will last approximately 17 months.

Expanded Cohort: Assuming a 1-month enrollment period, the initial phase will last approximately 13 months. The study duration including the revaccination stage will be approximately 25 months.

As the subjects in the initial phase of the expanded cohort will receive SIIV, this phase of the study is dependent on SIIV availability and access to subjects who have not received SIIV within the preceding 6 months. It is anticipated that this phase of the study will be conducted in the same geographic location as the sentinel phase; however, if required for operational reasons, it is possible that sites in the opposite hemisphere may be used, or that this phase of the study may be conducted over more than 1 influenza season or in more than 1 geographic location.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

For the revaccination stage, subject eligibility will be checked and reviewed for inclusion criteria 1, 2, 3, 4, and 7 and exclusion criteria 3 to 16.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all pertinent aspects of the study.

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

   Note: Healthy subjects with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

3. Willing and able to comply with scheduled visits, vaccination plan, laboratory tests, and other study procedures.

4. Male subject who is able to father children and willing to use a highly effective method of contraception as outlined in this protocol until at least 28 days after the last dose of investigational product; female subject who is of childbearing potential and at risk for pregnancy and who is willing to use a highly effective method of contraception as outlined in this protocol until at least 28 days after the last dose of investigational product; male subject not able to father children; female subject not of childbearing potential.

Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

5. **Sentinel-cohort subjects only:** Male and female adults 18 to 85 years of age at the time of enrollment (signing of the ICD).

6. **Expanded-cohort subjects only:** Male and female adults 18 to 49 years of age or 65 to 85 years of age at the time of enrollment (signing of the ICD).

7. **Expanded-cohort subjects for revaccination only:** Subjects in the 240-µg dose group and the placebo group who completed primary vaccinations at Visit 1 and Visit 2 and signed and dated the ICD for participating in the revaccination stage.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. **Sentinel-cohort subjects only:** Any screening hematology and/or blood chemistry laboratory value listed in Table 7 that meets the definition of a ≥ Grade 1 abnormality.

   Note: With the exception of bilirubin, subjects with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same subject.)

2. **Sentinel-cohort subjects only:** Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.

3. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4. Participation in other studies involving investigational product within 28 days prior to study entry and/or during study participation.

5. Known infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

6. Previous vaccination with any licensed or investigational RSV vaccine before enrollment into the study, or planned receipt throughout the study of nonstudy RSV vaccine.

7. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product(s), including natural rubber latex. In addition, for expanded-cohort subjects only, history of severe allergic reaction (eg, anaphylaxis) to any substance.

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

9. Subjects who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

10. Subject with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

11. Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration or planned receipt throughout the study.

12. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

14. Women who are pregnant or breastfeeding.

15. **Expanded-cohort subjects only (including subjects for revaccination):** Vaccination with any influenza vaccine within 6 months (182 days) before investigational product administration.

16. **Expanded-cohort subjects only (including subjects for revaccination):** Allergy to egg proteins (egg or egg products) or chicken proteins.

4.3. Criteria for Temporarily Delaying Vaccine Administration

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

1. Current febrile illness (oral temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before investigational product administration.

2. Any acute respiratory illness within 14 days before investigational product administration.

3. Receipt of any inactivated vaccine within 14 days or any live vaccine within 28 days before or anticipated receipt of any vaccine within the 14 days after investigational product administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Investigational product 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.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly until at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment until at least 28 days after the last dose of investigational product and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.5. 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.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. INVESTIGATIONAL PRODUCTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) are RSV vaccine and placebo (saline control).

Commercially available SIIV/SIIV high-dose (HD) will also be provided by the sponsor.

Subjects 18 to 49 years of age will receive SIIV. Subjects 65 to 85 years of age will be given either SIIV or SIIV HD depending on availability.

5.1. Allocation to Investigational Product

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). Site staff will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number and the subject number.

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

5.1.1. Blinding of Study Site Personnel

This is an observer-blinded study as the physical appearance of the RSV vaccine candidates, placebo and SIIV may differ.

The subject, investigator, study coordinator, and other site staff will be blinded. At the study site only the dispenser(s)/administrator(s) are unblinded. For the revaccination stage, the sponsor study team will provide sites a list of expanded-cohort subjects (the groups receiving the 240-µg dose level with or without $Al[OH]_3$ and the placebo group) who may be eligible for revaccination. The subject, investigator, study coordinator, and other site staff will remain blinded to the vaccine group of each subject.

Contact between the unblinded dispenser(s)/administrator(s) and study subjects should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispenser(s)/administrator(s) must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the investigational product.

5.1.2. Blinding of the Sponsor

The sponsor study team members will be blinded to the vaccine assigned/received by all subjects in the sentinel cohort, from subject randomization up until 1 month after vaccination when safety and immunogenicity data are available for analyses.

The sponsor study team members will be blinded to the vaccine assigned/received by subjects in the expanded cohort, from subject randomization up until 1 month after Vaccination 2 when safety and immunogenicity data are available for analyses. Prior to the revaccination stage, the sponsor study team will provide sites a list of expanded-cohort subjects (the groups receiving the 240-µg dose level with or without $Al(OH)_3$ and the placebo group) who may be eligible for revaccination.

Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study.

Certain sponsor personnel not directly involved in the conduct of the study will review safety data as defined in an IRC charter per Pfizer standard operating procedures (SOPs). Unblinded sponsor personnel who are not part of the study team will be assigned to assess whether a stopping rule is triggered and for ongoing safety review.

Those study team members who are involved in ensuring that protocol requirements for investigational product handling, allocation, and administration are fulfilled at the site (eg, study manager; clinical research associates [CRAs]) will be unblinded for the duration of the study.

5.2. Breaking the Blind

At the initiation of the study, the investigator will be instructed on the method for breaking the blind for an individual subject. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

The investigational product will be administered by the appropriately designated study staff at the investigator site.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

5.4.1.1. Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

CCI [redacted] The lyophilized drug product contains excipients which, after reconstitution, will yield a solution as detailed in Table 4 below.

There are 3 different presentations of RSV vaccine drug product representing 3 different dose levels of RSV antigen (60 μg, 120 μg, and 240 μg). The lyophilized cake is reconstituted by diluent with either sterile water for injection or a sterile suspension of $Al(OH)_3$ in water for injection.

The fill volume of the drug product vial and diluent vial are designed such that the intended vaccine dose is delivered in a 0.5-mL injection volume. CCI [redacted]

[redacted]

5.4.1.2. Seasonal Inactivated Influenza Vaccine

Commercially available quadrivalent SIIV will be used for subjects 18 to 49 years of age.

Commercially available HD trivalent SIIV (if available) or quadrivalent SIIV will be used for subjects 65 to 85 years of age.

Investigational sites will be provided with details of which commercially available SIIV or SIIV HD will be provided prior to the start of enrollment of the expanded cohort.

The World Health Organization may change its influenza vaccine reference strain recommendations from one northern or southern hemisphere influenza season to the next and may recommend more than 1 reference strain for each type A subtype or type B lineage; different national regulatory authorities may select different reference strains in a single season; and different SIIV manufacturers may choose different influenza vaccine strains that are antigenically like the selected reference strains. Therefore, the influenza vaccines that are available in different seasons and in different countries may have different strain compositions, and this study may necessarily include more than 1 SIIV formulation.

5.4.1.3. Placebo

The placebo for the RSV vaccines will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

The placebo for SIIV (expanded cohort only) will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

Placebo will be provided by the sponsor to each study site. Placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

5.4.2. Preparation and Dispensing

Investigational product preparation and dosing information will be provided in the investigational product (IP) manual.

The investigational product will be dispensed using an IRT investigational product management system.

5.5. Administration

Vaccine will be administered in the upper deltoid muscle by the **unblinded** administrator.

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 investigational products should be performed by an appropriately qualified, Good Clinical Practice (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.

Investigational product administration details will be recorded on the CRF.

5.5.1. Sentinel Cohort

Subjects in the sentinel cohort will receive 1 dose of either RSV vaccine with $Al(OH)_3$, RSV vaccine without $Al(OH)_3$, or placebo at Visit 1 in accordance with the randomization schedule.

RSV vaccine or placebo must be administered intramuscularly by injecting 0.5 mL into the deltoid muscle of the left arm.

Table 5. Sentinel Cohort; Location of Injection

Visit 1	
RSV	Left deltoid muscle
RSV+$Al(OH)_3$	Left deltoid muscle
Placebo	Left deltoid muscle

Abbreviations: $Al(OH)_3$ = aluminum hydroxide; RSV = respiratory syncytial virus vaccine.

5.5.2. Expanded Cohort

Subjects will receive 2 injections at Visit 1 and 1 injection at Visit 2 in accordance with the randomization schedule; see Table 6 below. In the revaccination stage, only subjects in the 240-µg dose groups and the placebo group will receive 2 injections at Visit 7 and 1 injection at Visit 8.

Table 6. Expanded Cohort; Location of Injection

Visit 1 and Visit 7[a]		Visit 2 and Visit 8[b]	
RSV SIIV	Left deltoid muscle Right deltoid muscle	Placebo	Deltoid muscle of nondominant arm
RSV Placebo	Left deltoid muscle Right deltoid muscle	SIIV	Deltoid muscle of nondominant arm
RSV+$Al(OH)_3$ SIIV	Left deltoid muscle Right deltoid muscle	Placebo	Deltoid muscle of nondominant arm
RSV+$Al(OH)_3$ Placebo	Left deltoid muscle Right deltoid muscle	SIIV	Deltoid muscle of nondominant arm
Placebo Placebo	Left deltoid muscle Right deltoid muscle	SIIV	Deltoid muscle of nondominant arm

a. Visit 7 is applicable only to the expanded-cohort subjects in the 240-µg dose groups and the placebo group.
b. Visit 8 is applicable only to the expanded-cohort subjects in the 240-µg dose groups and the placebo group.
Abbreviations: $Al(OH)_3$ = aluminum hydroxide; RSV = respiratory syncytial virus vaccine;
SIIV = seasonal inactivated influenza vaccine.

5.6. Investigational Product Storage

SIIV, investigational product, diluent, and placebo will be shipped at [redacted] to the study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, SIIV, investigational product, diluent, and placebo should be immediately transferred to a [redacted] temperature-monitored refrigerator for storage.

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, and SIIV or SIIV HD, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product once reconstituted.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). 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, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

5.8.1. Prohibited Nonstudy Vaccines Prior to the Study

- Licensed or investigational RSV vaccines at any time.
- Receipt of any inactivated vaccine within 14 days or any live vaccine within 28 days before investigational product administration.
- **Expanded-cohort subjects only:** Vaccination with any influenza vaccine within 6 months (182 days) before investigational product administration.

5.8.2. Prohibited Nonstudy Vaccines and Medications During the Study

- Nonstudy investigational vaccines, investigational drugs, or investigational medical devices are prohibited during the course of the study.
- Licensed or investigational RSV vaccines and blood/plasma products or immunoglobulins are prohibited during the course of the study.
- Immunosuppressive therapy is prohibited during the study, with the exception of inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids, which are permitted.
- Unless considered medically necessary, no vaccines should be administered until at least 28 days after investigational product administration.
- Prophylactic antipyretics and other pain medication to prevent symptoms associated with investigational product administration are not permitted.

5.8.3. Permitted Nonstudy Vaccines and Medications During the Study

- **Sentinel-cohort subjects only:** Licensed influenza vaccine may be given during the study starting 15 days after investigational product administration. If medically necessary (eg, pandemic or outbreak with pandemic potential), influenza vaccine may be given at any time.

- **Expanded-cohort subjects only:** Licensed influenza vaccine may be given during the study starting after the blood sample has been taken at Visit 3 in the primary vaccination stage and starting after Visit 9 in the revaccination stage. If medically necessary (eg, pandemic or outbreak with pandemic potential), influenza vaccine may be given at any time.

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

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during subject participation in the study.

- Medications other than those described as prohibited in Section 5.8.2 are permitted.

5.8.4. Recording Nonstudy Vaccinations and Concomitant Medications

The name and date of administration for all nonstudy vaccinations received will be collected and recorded in the CRF from the time of signing of the ICD to the 12-month follow-up visit (Visit 7 for sentinel-cohort subjects, Visit 6 for expanded-cohort subjects) and from the time of signing of the ICD for participating in the revaccination stage to the 12-month follow-up visit after revaccination (expanded-cohort subjects for revaccination).

Sentinel-cohort subjects only: Details of any current medications taken at baseline will be recorded in the CRF at Visit 0.

6. STUDY PROCEDURES

6.1. Sentinel Cohort, Visit 0 – Screening (Days -14 to -2 Prior to Vaccination)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the subject. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the subject. The source data must reflect that the informed consent was obtained before participation in the study.

- Assign single subject identifier using the IRT system.

- Obtain the subject demography (including date of birth, sex, race, and ethnicity). The date of birth will be collected to critically evaluate the immune response and safety profile by age.

- Assess and record tobacco usage.

- Obtain any medical history of clinical significance.

- Obtain details of any medications currently taken.

- Record nonstudy vaccinations as described in Section 5.8.4.
- Measure vital signs, including weight, height, sitting blood pressure, and pulse rate.
- Measure subject's temperature (oral).
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Verify understanding of and compliance with protocol requirements for contraception.
- Ensure that all inclusion criteria are met and that none of exclusion criteria 3 to 14 are met.
- Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments.
- Collect a blood sample (approximately 10 mL) to determine the subject's HIV, HBV, and HCV status.
- Record adverse events (AEs) as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

With the exception of bilirubin, if any Grade 1 hematology or blood chemistry abnormalities (as defined in Table 7) are found from samples taken at Visit 0 and the investigator believes the results to be erroneous or to represent a stable Grade 1 abnormality, a retest of the abnormal laboratory parameters may be conducted. Subjects with stable Grade 1 abnormalities may be considered eligible at the discretion of the investigator.

A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same subject.

If the subject is found ineligible for the study based on a full assessment of inclusion and exclusion criteria, the investigator may advise the subject, by telephone, that the subject will be withdrawn from further participation in the study. All eligible subjects will proceed to Visit 1.

6.2. Sentinel Cohort, Visit 1: Vaccination (Day 1)

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

- Review hematology and chemistry results.
- Ensure that all inclusion criteria and none of the exclusion criteria are met.
- Prior to vaccination, measure the subject's temperature (oral).
- Ensure that the subject meets none of the temporary delay criteria as described in Section 4.3.
- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.
- Prior to vaccination, collect a blood sample of approximately 100 mL for antibody assessment.
- Verify understanding of and compliance with protocol requirements for contraception.
- Obtain the subject's randomization number and investigational product kit number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer a single 0.5-mL injection of investigational product into the deltoid muscle of the left arm. Please refer to the IP manual for further instruction on this process.
- For the first site only, blinded site staff must observe the first 4 subjects in the 18- to 49-year-old age group for at least 4 hours after investigational product administration for any acute reactions. Thereafter, blinded site staff must observe subjects for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions in the subject's source documents, on the AE page of the CRF, and on a serious adverse event (SAE) form as applicable.
- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures and provide instructions on their use.
- Issue the subject an electronic diary (e-diary) and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination.

- Ask the subject to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 14 after vaccination to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site on the left arm measuring greater than 10 cm (>20 measuring device units).
  - Any blackening of the skin (necrosis) at the injection site on the left arm.
  - Any peeling/scaling of the skin (exfoliative dermatitis).
  - Severe pain at the injection site on the left arm.
  - Any severe systemic event.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind subjects that study staff may contact them to obtain additional information on events entered into the e-diary.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the investigational product accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate subject compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

6.3. Sentinel Cohort, Visit 2: 2-Week Follow-up Visit (14-18 Days After Visit 1)

- Ensure that the subject meets none of the withdrawal criteria as described in Section 6.23.
- Verify understanding of and compliance with protocol requirements for contraception.

- Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Review the subject's e-diary data and collect the e-diary. 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 if required.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.4. Sentinel Cohort, Visit 3: 1-Month Follow-up Visit (28-35 Days After Visit 1)

- Ensure that the subject meets none of the subject withdrawal criteria as described in Section 6.23.
- Review all hematology and chemistry results from the previous visit. The hematology and blood chemistry toxicity grading scales (Table 7) must be referenced when assessing a subject's laboratory results. Refer to Section 8.2.2 for details about reporting of laboratory abnormalities as an AE in the CRF.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 100 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.5. Sentinel Cohort, Visit 4: 2-Month Follow-up Visit (56-70 Days After Visit 1)

- Ensure that the subject meets none of the withdrawal criteria as described in Section 6.23.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.6. Sentinel Cohort, Visit 5: 3-Month Follow-up Visit (84-105 Days After Visit 1)

- Ensure that the subject meets none of the withdrawal criteria as described in Section 6.23.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.7. Sentinel Cohort, Visit 6: 6-Month Follow-up Visit (168-210 Days After Visit 1)

- Ensure that the subject meets none of the withdrawal criteria as described in Section 6.23.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.8. Sentinel Cohort, Visit 7: 12-Month Follow-up Visit (350-378 Days After Visit 1)

- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

6.9. Sentinel Cohort Subjects: Unscheduled Reactogenicity Visits

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

- redness at the injection site on the left arm measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site on the left arm measuring >20 measuring device units (>10.0 cm),
- any blackening of the skin (necrosis) at the injection site on the left arm,
- any peeling/scaling of the skin (exfoliative dermatitis),
- fever ≥102.1°F (≥39.0°C),
- severe injection site pain on the left arm,
- severe fatigue,
- severe headache,
- severe nausea,
- severe vomiting,
- severe diarrhea,
- severe muscle pain,
- severe joint pain.

A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The subject is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The subject recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).

This contact will be recorded in the subject's source notes and in the CRFs.

If the subject is unable to attend the unscheduled visit, 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, who will:

- Measure oral temperature.
- Measure the subject's pulse rate.
- Measure the subject's blood pressure (sitting).
- Measure the minimum and maximum diameters of redness on the left arm (if present).
- Measure the minimum and maximum diameters of swelling on the left arm (if present).
- Assess any blackening of the skin (necrosis) at the injection site on the left arm.
- Assess any peeling/scaling of the skin (exfoliative dermatitis).
- Assess any injection site pain on the left arm that is present in accordance with the reactogenicity grading scale provided in Section 7.5.2.
- Assess for lymphadenopathy associated with any local reaction.
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 7.5.3.
- Ask the subject if he/she attended an emergency room visit or was hospitalized.
- For severe pain at the injection site on the left arm associated with an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, or any necrosis or exfoliative dermatitis, the investigator must assess

these events in accordance with the severity AE grading scale provided in Section 8 for documentation on the AE CRF.

- Complete the source documents.

- The investigator or an authorized designee will complete the CRFs.

Subjects will be instructed to contact the site to report any significant illness, medically attended event, or hospitalization that occurs during the study period.

6.10. Expanded Cohort, Visit 1: Vaccination 1 (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the subject. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the subject. 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.

- Assign single subject identifier using the IRT system.

- Obtain the subject's demography (including date of birth, sex, race, and ethnicity). The date of birth will be collected to critically evaluate the immune response and safety profile by age.

- Assess and record tobacco usage.

- Obtain any medical history of clinical significance.

- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.

- Record nonstudy vaccinations as described in Section 5.8.4.

- Ensure and document that all of the inclusion criteria, and none of the exclusion criteria, are met Section 4).

- Prior to vaccination, measure the subject's temperature (oral).

- Ensure that the subject meets none of the temporary delay criteria as described in Section 4.3.

- Verify understanding of and compliance with protocol requirements for contraception.

- Obtain the subject's randomization number and investigational product kit number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.

- Obtain a midturbinate nasal swab.

- Prior to vaccination, collect a blood sample of approximately 50 mL for antibody assessment.

- Unblinded site staff member(s) will dispense/administer a 0.5-mL injection of investigational product into the deltoid muscle of the left arm and a 0.5-mL injection of investigational product into the deltoid muscle of the right arm (see Table 6). Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions in the subject's source documents, on the AE page of the CRF, and on an SAE form as applicable.

- Record AEs as described in Section 8.

- Issue a measuring device to measure local reactions at the injection site of the left arm and a digital thermometer for recording daily temperatures and provide instructions on their use.

- Issue the subject an e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination.

- Provide instructions on self-collection of midturbinate nasal swab(s).

- Ask the subject to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 14 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

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

    - Any blackening of the skin (necrosis) at the injection site on the left arm.

    - Any peeling/scaling of the skin (exfoliative dermatitis).

- Severe pain at the injection site on the left arm.
- Any severe systemic event.

Remind subjects that study staff may contact them to obtain additional information on events entered into the e-diary.

- Starting from Day 15 after the first vaccination (where Day 1 is the day of vaccination), remind the subject to self-collect a midturbinate nasal swab(s) if he or she experiences 1 or more of the following respiratory illness symptoms lasting longer than 24 hours and to contact the site staff or investigator immediately to determine if an unplanned illness visit for respiratory tract infection is required (see Section 6.17):
  - Sore throat.
  - New or increased cough.
  - New or increased nasal congestion.
  - New or increased nasal discharge.
  - New or increased wheezing.
  - New or increased shortness of breath.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the investigational product accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate subject compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

6.11. Expanded Cohort, Visit 2: Vaccination 2 (28 to 35 Days After Visit 1)

- Review the subject's e-diary data and collect the e-diary. 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 if required.

- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.
- Prior to vaccination, measure the subject's temperature (oral).
- Record nonstudy vaccinations as described in Section 5.8.4. Ensure that the subject meets none of the temporary delay criteria as described in Section 4.3.
- Verify understanding of and compliance with protocol requirements for contraception.
- Prior to vaccination, collect a blood sample of approximately 50 mL for antibody assessment.
- If the subject continues to be eligible for the study, obtain the subject's investigational product container number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer a single 0.5-mL injection of investigational product into the deltoid muscle of the nondominant arm (SIIV or SIIV HD or placebo). Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions in the subject's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Record AEs as described in Section 8.
- Remind the subject to self-collect a midturbinate nasal swab(s) if he or she experiences 1 or more of the following respiratory illness symptoms lasting longer than 24 hours and to contact the site staff or investigator immediately to determine if an unplanned illness visit for respiratory tract infection is required (see Section 6.17):
    - Sore throat.
    - New or increased cough.
    - New or increased nasal congestion.
    - New or increased nasal discharge.
    - New or increased wheezing.
    - New or increased shortness of breath.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the investigational product accountability records.

6.12. Expanded Cohort, Visit 3: 2-Month Follow-up Visit (56-70 Days After Visit 1)

- Ensure that the subject meets none of the subject withdrawal criteria as described in Section 6.23.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind the subject to self-collect a midturbinate nasal swab(s) if he or she experiences 1 or more of the following respiratory illness symptoms lasting longer than 24 hours and to contact the site staff or investigator immediately to determine if an unplanned illness visit for respiratory tract infection is required (see Section 6.17):
    - Sore throat.
    - New or increased cough.
    - New or increased nasal congestion.
    - New or increased nasal discharge.
    - New or increased wheezing.
    - New or increased shortness of breath.

6.13. Expanded Cohort, Visit 4: 3-Month Follow-up Visit (84-105 Days After Visit 1)

- Ensure that the subject meets none of the withdrawal criteria as described in Section 6.23.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind the subject to self-collect a midturbinate nasal swab(s) if he or she experiences 1 or more of the following respiratory illness symptoms lasting longer than 24 hours and to contact the site staff or investigator immediately to determine if an unplanned illness visit for respiratory tract infection is required (see Section 6.17):
    - Sore throat.
    - New or increased cough.
    - New or increased nasal congestion.
    - New or increased nasal discharge.
    - New or increased wheezing.
    - New or increased shortness of breath.

6.14. Expanded Cohort, Visit 5: 6-Month Follow-up Visit (168-210 Days After Visit 1)

- Ensure that the subject meets none of the subject withdrawal criteria as described in Section 6.23.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.15. Expanded Cohort, Visit 6: 12-Month Follow-up Visit (350-378 Days After Visit 1)

- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

6.16. Expanded Cohort: Unscheduled Reactogenicity Visits Following Vaccination 1

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

- redness at the injection site on the left arm measuring >20 measuring device units (>10.0 cm),
- swelling at the injection site on the left arm measuring >20 measuring device units (>10.0 cm),
- any blackening of the skin (necrosis) at the injection site on the left arm,
- any peeling/scaling of the skin (exfoliative dermatitis),
- fever ≥102.1°F (≥39.0°C),
- severe injection site pain on the left arm,
- severe fatigue,
- severe headache,
- severe nausea,
- severe vomiting,
- severe diarrhea,
- severe muscle pain,
- severe joint pain.

A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The subject is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The subject recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).

This contact will be recorded in the CRF and in the subject's source documentation.

If the subject is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit.

The reaction(s) 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, who will:

- Measure oral temperature.
- Measure the subject's pulse rate.
- Measure the subject's blood pressure (sitting).
- Measure the minimum and maximum diameters of redness on the left arm (if present).
- Measure the minimum and maximum diameters of swelling on the left arm (if present).
- Assess any blackening of the skin (necrosis) at the injection site on the left arm.
- Assess any peeling/scaling of the skin (exfoliative dermatitis).
- Assess any injection site pain on the left arm that is present in accordance with the reactogenicity grading scale provided in Section 7.5.2.
- Assess for lymphadenopathy associated with any local reaction.
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 7.5.3.
- Ask the subject if he/she attended an emergency room visit or was hospitalized.

- For severe pain at the injection site on the left arm associated with an emergency room visit or hospitalization, severe systemic events, associated with an emergency room visit or hospitalization, or any necrosis or exfoliative dermatitis, the investigator must assess these events in accordance with the severity AE grading scale provided in Section 8 for documentation on AE CRF.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

Subjects will be instructed to contact the site to report any significant illness, medically attended event, or hospitalization that occurs during the study period.

6.17. Expanded Cohort: Surveillance for Respiratory Illness

- Starting from Day 15 after the first vaccination (where Day 1 is the day of vaccination) until Visit 5, the subject should self-collect a midturbinate nasal swab(s) if he or she experiences 1 or more of the following respiratory illness symptoms lasting longer than 24 hours and contact the site staff or investigator immediately to determine if an unplanned illness visit for respiratory tract infection is required. The contact may be by an electronic method of communication (including but not limited to electronic messaging, text, email), by phone call, or by face-to-face contact.

- Complete the source documents.

- Continue this surveillance contact approximately every week until Visit 5.

- The sponsor may increase or decrease the frequency of the weekly contacts or the duration of surveillance for respiratory illness based on RSV surveillance data or other operational factors.

If appropriate, the sponsor will inform the study centers of any changes to the frequency of reminder contacts or changes to the duration of surveillance.

6.17.1. Expanded Cohort: Respiratory Illness Visit Criteria

Starting from Day 15 after the first vaccination (where Day 1 is the day of vaccination) until Visit 5, if the subject experiences 1 or more of the following respiratory illness symptoms lasting longer than 24 hours, a contact should occur as soon as possible between the subject and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled respiratory illness visit is required.

- Sore throat.

- New or increased cough.

- New or increased nasal congestion.

- New or increased nasal discharge.
- New or increased wheezing.
- New or increased shortness of breath.

6.17.2. Expanded Cohort: Conduct of the Respiratory Illness Visit (Within 7 Days After Onset of Respiratory Tract Infection)

- If the respiratory illness criteria are met, the investigator or a medically qualified member of the study site staff will determine if the subject should attend a respiratory illness visit. If the site determines that a respiratory illness visit is required, the subject will be seen in the clinic or home, ideally within 7 days after the onset of the illness. If an illness visit cannot be arranged within 7 days after the onset of the illness, a visit should still be performed as soon as possible.
- Collect 1 midturbinate nasal swab.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Obtain the details of the diagnosis and document them on an AE CRF; resolution of the illness must be confirmed at subsequent study visits.
- Obtain details of any respiratory symptoms: sore throat, cough, nasal congestion, nasal discharge, wheezing, shortness of breath, as well as details of fever, muscle pain, joint pain.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

6.17.3. Expanded Cohort: Conduct of the Unplanned Respiratory Convalescent Visit (28 to 35 Days After Respiratory Illness Visit)

- Collect 1 midturbinate nasal swab from the subject.
- Collect ~50 mL of blood for antibody assessment.
- Obtain details of the date of resolution of any respiratory symptoms: sore throat, cough, nasal congestion, nasal discharge, wheezing, shortness of breath, as well as details of fever, muscle pain, joint pain.
- Record nonstudy vaccinations as described in Section 5.8.4.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs, including updating the AE CRF with the resolution date of the respiratory tract infection.

6.18. Expanded-Cohort Subjects for Revaccination, Visit 7: Vaccination 3 (350-420 Days After Visit 1)

Visit 6 and Visit 7 can be conducted on the same day. Complete all required procedures for Visit 6 before performing procedures for Visit 7.

Before any study-related procedures are performed for Visit 7, voluntary, written study-specific informed consent will be obtained from the subject. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the subject. The source data must reflect that the informed consent was obtained before participation in the revaccination stage of the study.

- Perform physical examination to confirm the subject's eligibility.

- Prior to revaccination, perform a urine pregnancy test for female subjects of childbearing potential.

- Record nonstudy vaccinations as described in Section 5.8.4.

- Ensure and document that all of the inclusion criteria, and none of the exclusion criteria, are met (Section 4).

- Prior to vaccination, measure the subject's temperature (oral).

- Ensure that the subject meets none of the temporary delay criteria as described in Section 4.3.

- Verify understanding of and compliance with protocol requirements for contraception.

- Obtain the subject's investigational product kit number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.

- Prior to vaccination, collect a blood sample of approximately 50 mL for antibody assessment **only** if Visit 6 and Visit 7 are not conducted on the same day.

- Unblinded site staff member(s) will dispense/administer a 0.5-mL injection of investigational product into the deltoid muscle of the left arm and a 0.5-mL injection of investigational product into the deltoid muscle of the right arm (see Table 6). Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions in the subject's source documents, on the AE page of the CRF, and on an SAE form as applicable.

- Record AEs as described in Section 8.

- Issue a measuring device to measure local reactions at the injection site of the **left** arm and a digital thermometer for recording daily temperatures and provide instructions on their use.

- Issue the subject an e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination.

- Ask the subject to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 14 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

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

  - Any blackening of the skin (necrosis) at the injection site on the left arm.

  - Any peeling/scaling of the skin (exfoliative dermatitis).

  - Severe pain at the injection site on the left arm.

  - Any severe systemic event.

- Remind subjects that study staff may contact them to obtain additional information on events entered into the e-diary.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Schedule an appointment for the subject to return for the next study visit.

- Remind the subject to bring the completed e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the investigational product accountability records.

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

6.19. Expanded-Cohort Subjects for Revaccination, Visit 8: Vaccination 4 (28-35 Days After Visit 7)

- Review the subject's e-diary data and collect the e-diary. 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 if required.

- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.

- Prior to vaccination, measure the subject's temperature (oral).

- Record nonstudy vaccinations as described in Section 5.8.4. Ensure that the subject meets none of the temporary delay criteria as described in Section 4.3.

- Verify understanding of and compliance with protocol requirements for contraception.

- Prior to vaccination, collect a blood sample of approximately 50 mL for antibody assessment.

- If the subject continues to be eligible for the study, obtain the subject's investigational product container number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.

- Unblinded site staff member(s) will dispense/administer a single 0.5-mL injection of investigational product into the deltoid muscle of the nondominant arm (SIIV or SIIV HD or placebo). Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions in the subject's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Record AEs as described in Section 8.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Schedule an appointment for the subject to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the investigational product accountability records.

6.20. Expanded-Cohort Subjects for Revaccination, Visit 9: 2-Month Follow-up Visit (56-70 Days After Visit 7)

- Ensure that the subject meets none of the subject withdrawal criteria as described in Section 6.23.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.21. Expanded-Cohort Subjects for Revaccination, Visit 10: 6-Month Follow-up Visit (168-210 Days After Visit 7)

- Ensure that the subject meets none of the subject withdrawal criteria as described in Section 6.23.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

6.22. Expanded-Cohort Subjects for Revaccination, Visit 11: 12-Month Follow-up Visit (350-378 Days After Visit 7)

- Collect a blood sample of approximately 50 mL for antibody assessment.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

6.23. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent 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.

Subjects who withdraw after randomization will not be replaced.

Lost to Follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or emails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. The site staff and representative may consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

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

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

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening (sentinel cohort only) and immediately before administration of each vaccine dose. A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product.

7.2. Biological Samples

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 subject'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 may be stored for up to 20 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 testing of the subject's genetic material will be performed.

Detailed information relating to nasal swab sample collection, processing, and storage can be found in the study reference manual (SRM) or equivalent manual.

The subject may request that his or 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 testing of the subject's genetic material is performed.

7.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events and hematology and blood chemistry laboratory assessments as described below are derived from the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[22]

7.2.2. HIV, Hepatitis B Surface Antigen (HBsAg), and Hepatitis C Serology Testing

At the screening visit (Visit 0, sentinel cohort only), approximately 10 mL of blood will be drawn to determine the subject's HIV status and rule out infection with HBV or HCV. The results from these tests will be available and reviewed at Visit 1.

7.2.3. Hematology and Blood Chemistry

Blood samples for hematology and blood chemistry assessments (approximately 10 mL) will be collected for all sentinel-cohort subjects at Visit 0 and Visit 2.

Assessments will include:

- Hematology: Hemoglobin, complete blood count with differential, and platelets.
- Blood chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.

For each of these assessments, postvaccination values will be compared to prevaccination values. Potential cases of drug-induced liver injury will be assessed as described in Section 8.4.2.

Repeat testing of the protocol-required laboratory parameters is permitted to confirm results. Additional laboratory testing not specified in the protocol may be performed at the discretion of the investigator as follow-up to an AE and should be recorded in the subject's source documents.

Table 7. Hematology and Blood Chemistry Toxicity Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Male hemoglobin (Hb)	12.5-13.5 g/dL (125-135 g/L)	10.5-12.4 g/dL (105-124 g/L)	8.5-10.4 g/dL (85-104 g/L)	<8.5 g/dL (<85 g/L)
Female hemoglobin (Hb)	11.0-12.0 g/dL (110-120 g/L)	9.5-10.9 g/dL (95-109 g/L)	8.0-9.4 g/dL (80-94 g/L)	<8.0 g/dL (<80 g/L)
Leukocyte increase (total WBCs)	10.8-15.0 × 10^9/L (× 10^3/μL)	>15.0-20.0 × 10^9/L (× 10^3/μL)	>20.0-25.0 × 10^9/L (× 10^3/μL)	>25.0 × 10^9/L (× 10^3/μL)
Leukocyte decrease (total WBCs)	2.5-3.5 × 10^9/L (× 10^3/μL)	1.5-<2.5 × 10^9/L (× 10^3/μL)	1.0-<1.5 × 10^9/L (× 10^3/μL)	<1.0 × 10^9/L (× 10^3/μL)
Neutrophil decrease (absolute neutrophil count)	1.5-2.0 × 10^9/L (× 10^3/μL)	1.0-<1.5 × 10^9/L (× 10^3/μL)	0.5-<1.0 × 10^9/L (× 10^3/μL)	<0.5 × 10^9/L (× 10^3/μL)
Platelets	125-140 × 10^9/L (× 10^3/μL)	100-124 × 10^9/L (× 10^3/μL)	25-99 × 10^9/L (× 10^3/μL)	<25 × 10^9/L (× 10^3/μL)
Alanine aminotransferase (ALT)	1.1-2.5 × ULN	2.6-5.0 × ULN	5.1-10.0 × ULN	>10 × ULN
Aspartate aminotransferase (AST)	1.1-2.5 × ULN	2.6-5.0 × ULN	5.1-10.0 × ULN	>10 × ULN
Alkaline phosphatase	1.1-2.0 × ULN	2.1-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Total bilirubin (in presence of ALT or AST abnormality)	1.1-1.25 × ULN	1.26-1.5 × ULN	1.51-1.75 × ULN	> 1.75 × ULN
Total bilirubin (in presence of normal ALT and AST)	1.1-1.5 × ULN	1.6-2.0 × ULN	2.0-3.0 × ULN	> 3.0 × ULN
Blood urea nitrogen (BUN)	23-26 mg/dL	27 – 31 mg/dL	> 31 mg/dL	Requires dialysis
Creatinine	1.5-1.7 mg/dL	1.8-2.0 mg/dL	2.1-2.5 mg/dL	>2.5 mg/dL or requires dialysis

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

7.3. Immunogenicity

Blood samples (approximately 50 or 100 mL/visit) will be collected as detailed in Section 6.

Sentinel Cohort: The total volume of blood collected from each sentinel-cohort subject for antibody assessment will be approximately 450 mL (~50 or 100 mL/visit) over the course of the 1-year study. Sera will be used for immunogenicity assessments and assay development purposes.

Expanded Cohort: The total volume of blood collected from each expanded-cohort subject for antibody assessment will be approximately 300 mL (~50 mL/visit) over the course of the first 1-year part of the study, plus 2 additional 50-mL blood samples per illness episode (~100 mL per respiratory illness). An additional ~200 mL or ~250 mL (~50 mL/visit) of blood will be collected from the revaccination subjects over the course of the second 1-year part of the study.

Sera will be used for additional vaccine and infectious disease-related research, including immunogenicity assessments and assay development purposes.

Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual. All assays will be performed at Vaccine Research and Development (VRD), located at 401 North Middletown Road, Pearl River, NY 10965 and/or at a facility designated by Pfizer.

7.3.1. RSV and Influenza Vaccine Antibody Testing

Sera collected from both the sentinel and expanded cohorts will be assayed for RSV A– and RSV B–neutralizing antibody levels, CCI [redacted]. RSV A– and RSV B–neutralizing antibody levels will be determined for each blood sample and reported as the neutralizing titer. CCI [redacted]

CCI [redacted] In the expanded-cohort subjects only, hemagglutination inhibition antibody titers will be measured by the standard HAI for the influenza vaccine strains contained in the vaccine. CCI [redacted] Testing will be performed by a facility designated by Pfizer.

CCI [redacted]

7.4. Respiratory Pathogens

A midturbinate swab will be collected from each subject in the expanded cohort during Visit 1 in order to describe the frequency of baseline RSV shedding prior to the administration of the investigational product.

Subjects will be asked to take a midturbinate nasal swab when they have experienced 1 or more signs or symptoms of a respiratory illness for longer than 24 hours. Subjects will be permitted to take more than 1 swab if they consider their symptoms have worsened.

In addition to the nasal swab that the subjects collect, additional midturbinate swabs will be collected during any unplanned respiratory illness visits.

Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual. All assays will be performed at Vaccine Research and Development (VRD), located at 401 North Middletown Road, Pearl River, NY 10965 and/or at a facility designated by Pfizer. Samples will be analyzed for RSV A and RSV B and other respiratory pathogens by polymerase chain reaction (PCR)-based assays. Additional exploratory analyses may also be performed.

7.5. Safety Parameters

Safety parameters will be assessed as described in the schedule of activities and below.

A medical history and physical examination will be performed on all subjects, to establish a baseline. Significant medical history and observations from the physical examination will be documented in the CRF.

The safety parameters include e-diary reports of local reactions and systemic events that occur in the 14 days after investigational product administration at Visit 1 and Visit 7. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 7.5.2 and Section 7.5.3.

For the first site only, blinded site staff must observe the first 4 subjects in the 18- to 49-year-old age group for at least 4 hours after investigational product administration for any acute reactions. Thereafter, blinded site staff must observe subjects for at least 30 minutes after investigational product administration for any acute reactions. Acute reactions after investigational product administration will be assessed and documented in the AE CRF.

In addition, AEs, medically attended adverse events (MAEs), and SAEs are collected, recorded, and reported as defined in Section 8. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

7.5.1. Subject Electronic Diary

The subject will be asked to monitor and record local reactions, systemic events, fever, and antipyretics/pain medication used to treat symptoms, each evening for 14 days following vaccination at Visit 1 and Visit 7 (Day 1 through Day 14, where Day 1 is the day of vaccination). The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, systemic events, and antipyretics/pain medication used to treat symptoms recorded on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

These data do not need to be recorded by the investigator in the CRF. However, if a subject 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.

Investigators (or appropriately qualified designees) are required to review the e-diary data online to evaluate subject compliance and as part of the ongoing safety review (see Stopping Rules in Section 7.6).

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.

7.5.2. Local Reactions

Following vaccination at Visit 1 and Visit 7 (Day 1 through Day 14, where Day 1 is the day of vaccination), subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening. Subjects will also record any peeling/scaling (exfoliative dermatitis) or blackening of the skin (necrosis) at the injection site.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 8 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm.

A subject with severe redness, swelling, or pain or any peeling/scaling (exfoliative dermatitis) or blackening of the skin (necrosis) at the injection site will be prompted to contact the investigator to perform an unscheduled visit to assess the reaction.

Only an investigator is able to classify a subject's local reaction as Grade 4, after clinical evaluation of the subject 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 subject. If a subject experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected as an AE on the CRF. The event will be graded using the AE severity grading scale (Section 8.3).

Site staff will educate the subject regarding signs and symptoms that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

If a local reaction persists beyond the end of the e-diary period, the subject 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 subject's source notes and CRF.

Table 8. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Redness	2.5 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	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis
Pain (at the injection site)	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Grade 4 assessment should be made by the investigator using the AE severity grading scale. The assessment will be collected on the AE case report form.

7.5.3. Systemic Events

Following vaccination at Visit 1 and Visit 7 (Day 1 through Day 14, where Day 1 is the day of vaccination), subjects will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the subject according to the grading scale in Table 9 below. Subjects will also be instructed to contact site staff if they experience any Grade 3 prompted systemic event or if they visit the emergency room or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain within 14 days after vaccination at Visit 1 and Visit 7. Study staff may also contact the subject to obtain additional information on events entered into the e-diary.

Only an investigator is able to classify a subject's systemic event as Grade 4, after clinical evaluation of the subject or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the subject. If a subject experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. The procedure for notification of the sponsor is provided in the study documentation.

Further, if a systemic event persists beyond the end of the e-diary period, the subject 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 CRF.

Table 9. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires 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. Grade 4 assessment should be made by the investigator using the AE severity grading scale. The assessment will be collected on the AE case report form.

7.5.4. Fever

A digital thermometer will be given to the subject with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 14 days following vaccination at Visit 1 and Visit 7 (Day 1 through Day 14, where Day 1 is the day of vaccination) and at any time during the 14 days following vaccination at Visit 1 and Visit 7 that fever is suspected. Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary.

In the event of a fever on Day 14, temperature will be measured daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF.

A subject with a fever >102°F (38.9°C) will be prompted to contact the investigator. The investigator or designee will assess the fever and perform an unscheduled visit as appropriate.

Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 10 below.

Table 10. Ranges for Fever

Fever	38.0°C to 38.4°C 100.4°F to 101.1°F	38.5°C to 38.9°C 101.2°F to 102.0°F	39.0°C to 40.0°C 102.1°F to 104.0°F	>40.0°C >104.0°F

7.5.5. Use of Antipyretic/Pain Medication

For 14 days following vaccination at Visit 1 and Visit 7 (Day 1 through Day 14, where Day 1 is the day of vaccination), the subject will be asked to record the use of antipyretic and/or pain medication in the e-diary.

7.6. Stopping Rules

Hematology, blood chemistry, AE data, and e-diary reactogenicity data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

If it is suspected that a stopping rule has been met based on blinded safety assessment, the sponsor's designated unblinded personnel will decide whether a stopping rule has been met based on unblinded randomization information.

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

- The IRC will review all appropriate data.
- The stopping rule will PAUSE all randomization and RSV vaccination.
- The E-DMC will be informed.
- For all subjects vaccinated, all other routine study conduct activities, including SIIV vaccination where appropriate, ongoing data entry, reporting of AEs, subject e-diary completion, blood sample collection, and subject follow-up, will continue during the pause.

A stopping rule is met if any of the following events occur after administration of the investigational RSV vaccine at Visit 1. E-diary data confirmed by the investigator as being entered by the subject in error will not contribute toward a stopping rule.

Both formulations (with and without $Al[OH]_3$) at a given dose will be evaluated for contribution to stopping rules together. **Each age group will be assessed separately.** However, it is possible that the recommendations may include halting or continuing randomization with either or both formulations at a given dose.

Sentinel Cohort:

1. If any RSV-vaccinated subject develops an SAE that is assessed as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any RSV-vaccinated subject develops a Grade 4 local reaction or systemic event within 14 days after Vaccination 1 that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any RSV-vaccinated subject develops a fever >104.0°F (40°C) for at least 1 daily measurement within 14 days after Vaccination 1 that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any RSV-vaccinated subject develops a confirmed Grade 4 laboratory abnormality from the Visit 2 blood sample. Refer to Table 7, for details.

5. If ≥2 RSV-vaccinated subjects (**at any dose level**) report the same or similar severe (Grade 3) AE within 14 days after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

6. If ≥4 RSV-vaccinated subjects (**at a given dose level)** experience the same Grade 3 local reaction or systemic event within 14 days after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

7. If ≥4 RSV-vaccinated subjects in the sentinel cohort (**at a given dose level)** experience fever between 102.1°F and 104.0°F (39.0°C to 40.0°C) within 14 days after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

Expanded Cohort:

1. If any RSV-vaccinated subject develops an SAE that is assessed as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any RSV-vaccinated subject develops a Grade 4 local reaction or systemic event within 14 days after Vaccination 1 that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any RSV-vaccinated subject develops a fever >104.0°F (40°C) for at least 1 daily measurement within 14 days after Vaccination 1 that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If ≥3 RSV-vaccinated subjects (**at any dose level**) report the same or similar severe (Grade 3) AE within 14 days after Vaccination 1, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

7.6.1. Randomization and Vaccination After a Stopping Rule Is Met

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

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of vaccine group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

To be able to identify and clarify stopping rules, when the investigator becomes aware of a related SAE or a severe related AE, the investigator must immediately contact the Pfizer study physician directly. This procedure does not replace any of the standard AE recording and reporting requirements as described in the following sections.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a nonleading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (See Also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 3. From Visit 3 until the subject completes the study at 12 months after Vaccination 1 (Visit 7 for the sentinel cohort and Visit 6 for the expanded cohort), MAEs and SAEs will be collected. In addition, stop dates will be collected for any AEs ongoing at Visit 3.

The active AE and SAE collection period for each subject in the revaccination stage is from the time the subject provides informed consent for participating in the revaccination stage through and including Visit 9.

From Visit 9 until the subject completes the revaccination stage (Visit 11), MAEs and SAEs will be collected. In addition, stop dates will be collected for any AEs ongoing at Visit 9.

Any AE occurring up to 48 hours after the blood draws at Visit 4, 5, 6 (expanded- and sentinel-cohort subjects), or 7 (sentinel-cohort subjects only), Visit 10 or 11 (expanded-cohort subjects for revaccination), or the respiratory illness visit (expanded-cohort subjects only) must be recorded and reported in the CRF. Details of respiratory illness symptoms that meet the criteria for an unplanned respiratory illness visit will be collected from 15 days after Vaccination 1 until Visit 5 in all expanded-cohort subjects.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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 CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;

- A permanent impairment of a body function or permanent damage to a body structure;

- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

- Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;

- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric

wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

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 subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	SEVERE	Interferes significantly with subject's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections and will be handled as SAEs in the safety database.

8.4.2. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in the expanded cohort. However, should an investigator deem it necessary to assess LFTs because a subject 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 total bilirubin (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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase, and acetaminophen drug and/or protein adduct levels. 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 (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, 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 and liver imaging (eg, biliary tract) 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.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report 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

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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 immediately.

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 an AE page of the CRF.

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

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;

- The administration of an incorrect dosage;

- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

Medical device complaints that are not associated with an SAE, ie, for marketed/registered products, should be forwarded to Pfizer Global Manufacturing; and for medical device products not yet approved/registered anywhere in the world, forward product complaints to Pharmaceutical Sciences.

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and additional details will be documented in the statistical analysis plan (SAP) which is 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.

All of the safety, tolerability, and immunogenicity data will be summarized for the sentinel cohort and expanded cohort separately for each age group as well as for the combined age group within each cohort. In addition, sentinel and expanded cohorts will be combined and analyzed together by vaccine group as appropriate.

All analyses for both immunogenicity and safety data will be of descriptive nature.

9.1. Sample Size Determination

This Phase 1/2 FIH study is designed to describe the safety, tolerability, and immunogenicity of RSV-vaccine formulations in 2 age groups: 1) younger age group (18 to 49 years of age in the sentinel and expanded cohorts) and 2) older age group (50 to 85 years of age in the sentinel cohort and 65 to 85 years of age in the expanded cohort).

Sample size is not based on any formal statistical hypothesis testing. A total of up to approximately 1182 subjects 18 to 85 years of age (591 subjects in the younger age group and 591 subjects in the older age group) will be randomized with up to approximately 168 subjects in the sentinel cohort and up to approximately 1014 subjects in the expanded cohort. Within each age group, 12 subjects in the sentinel cohort and 39 subjects in the expanded cohort will be randomized for each vaccine group. Refer to Table 1 and Table 2 for a detailed description of the number of subjects per group. Refer to Table 3 for the approximate number of subjects in the expanded cohort who will be invited to participate in the revaccination stage.

For safety outcomes, Table 11 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 5%, with 24 subjects in the sentinel cohort at a dose level (12 for each formulation), there is 71% probability of observing at least 1 AE.

Table 11. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=24	N=39	N=48	N=78	N=102	N=180	N=540
0.5%	0.06	0.11	0.18	0.21	0.32	0.40	0.59	0.93
1%	0.11	0.21	0.32	0.38	0.54	0.64	0.84	>0.99
2%	0.22	0.38	0.55	0.62	0.79	0.87	0.97	>0.99
3%	0.31	0.52	0.70	0.77	0.91	0.96	>0.99	>0.99
5%	0.46	0.71	0.87	0.91	0.98	>0.99	>0.99	>0.99

Note: In the sentinel cohort, 24 subjects are planned to be vaccinated with a specific dose level of RSV vaccine (12/formulation/age group) and 48 subjects are the combined subjects from a specified dose level of RSV vaccine across age groups (12/formulation). In the expanded cohort, 78 subjects are planned to be vaccinated with a specific RSV vaccine formulation across age groups (39/formulation/age group). 102 subjects from both cohorts are combined for a specific formulation in a given dose level of RSV vaccine across age groups. In the entire study, a total of 180 subjects are planned to be vaccinated with a specific dose level of RSV vaccine from both cohorts within each age group and 540 subjects are the combined subjects from all dose levels of RSV vaccine within each age group.

Sample size for the revaccination stage is dependent upon the number of subjects providing consent to continue in the study.

9.2. Immunogenicity Analysis

Immunogenicity results will be analyzed separately for all the formulations in the sentinel cohort and in the expanded cohort for each age group. Within each age group in the sentinel cohort, all subjects who receive placebo will be combined as the control group.

Within each cohort, immunogenicity results will be summarized by formulation and dose level for the sentinel cohort, and summarized by formulation, dose level, and vaccination sequence for the expanded cohort.

In addition, immunogenicity results from sentinel and expanded cohorts will be combined and analyzed together as appropriate. For each age group at a given dose level, immunogenicity results of up to 1 month after vaccination from the subjects in the sentinel cohort will be combined with the results of up to 1 month after Vaccination 1 from the subjects in the expanded cohort who receive the same RSV vaccine formulation plus placebo at Vaccination 1. For example, in the RSV 60-μg dose level, RSV vaccine 60 μg (sentinel cohort) combines with RSV vaccine 60 μg/placebo+SIIV (expanded cohort); RSV vaccine 60 μg+$Al(OH)_3$ (sentinel cohort) combines with RSV vaccine 60 μg+$Al(OH)_3$/placebo+SIIV (expanded cohort).

9.2.1. Immunogenicity Analysis Populations

For the immunogenicity analyses, 2 analysis populations will be defined for the sentinel cohort and 3 analysis populations will be defined for both the expanded cohort and the expanded-cohort revaccination stage.

Sentinel Cohort:

1. **Evaluable immunogenicity population:** In general, the subject must have been eligible for the study, have received the RSV vaccine or placebo to which the subject was randomized, have had blood drawn within the prespecified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

2. **Modified intent-to-treat (mITT) population:** A subject must have been randomized and have at least 1 valid and determinate assay result related to the proposed analysis.

Expanded Cohort:

1. **Evaluable immunogenicity population for non-HAI analysis:** In general, the subject must have been eligible for the study, have received Vaccination 1 to which they were randomized, have had blood drawn within the prespecified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

2. **Evaluable immunogenicity population for HAI analysis:** In general, the subject must have been eligible for the study, have received the vaccination sequence to which they were randomized, have had blood drawn within the prespecified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

3. **mITT population:** A subject must have been randomized and have at least 1 valid and determinate assay result related to the proposed analysis.

Expanded-Cohort Revaccination Stage:

1. **Evaluable immunogenicity population for non-HAI analysis:** In general, the subject must have been eligible for the study, have received all Vaccinations 1, 2, and 3 to which he or she was randomized, have had blood drawn within the prespecified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

2. **Evaluable immunogenicity population for HAI analysis:** In general, the subject must have been eligible for the study, have received Vaccinations 1, 2, 3, and 4 to which he or she was randomized, have had blood drawn within the prespecified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

3. **mITT population:** A subject must have been randomized and have at least 1 valid and determinate assay result related to the proposed analysis.

The immunogenicity data will be summarized for each formulation as received for the evaluable immunogenicity population and as randomized for the mITT population. The evaluable immunogenicity population will be the primary analysis population for immunogenicity results.

9.2.2. Analysis of Immunogenicity Endpoints

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. Geometric mean titers (GMTs) and associated 2-sided 95% confidence intervals (CIs) will be calculated at each available time point for each vaccine group. CIs will be calculated by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using Student's t distribution.

Geometric mean fold rises (GMFRs) and associated 2-sided 95% CIs will be provided for RSV A– and RSV B–neutralizing antibody titers from before Vaccination 1 to each available time point through the 12-month follow-up visit. For expanded-cohort subjects participating in the revaccination stage, GMFRs and associated 2-sided 95% CIs will be provided for RSV A– and RSV B–neutralizing antibody titers from before revaccination to each available time point through 12 months after revaccination, and from 1 month after Vaccination 1 to 1 month after Vaccination 3. In addition, GMFRs and associated 2-sided 95% CIs will be provided for RSV A– and RSV B–neutralizing antibody titers from before Vaccination 1 to each available time point through 12 months after Vaccination 3. The GMFR will be calculated as the mean difference of individual subject logarithmically transformed antibody levels and back transformed to the original units. Two (2)-sided 95% CIs are also computed by back transformation of the CIs using 1-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.

Geometric mean ratios (GMRs) and associated 2-sided 95% CIs will be calculated for RSV A– and RSV B–neutralizing antibody titers between sera drawn from subjects vaccinated with RSV vaccine with or without concomitant SIIV at 1 month after Vaccination 1 in the expanded cohort. The GMR will also be computed for HAI for strains in SIIV by comparing sera drawn from subjects vaccinated with SIIV concomitantly with RSV vaccine at 1 month after Vaccination 1 or with SIIV alone at 1 month after Vaccination 2 in the expanded cohort. For expanded-cohort subjects participating in the revaccination stage, GMRs after revaccinations will be calculated in a similar way. The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units. Two (2)-sided 95% CIs are also computed by back transformation of the CIs using 2-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.

Seroprotection in HAI titers is defined as the percentage of subjects achieving an HAI antibody titer ≥1:40. The percentage of subjects achieving a seroprotection at 1 month after vaccination will be computed for each virus strain contained in SIIV separately.

Seroconversion in HAI titers is defined as the percentage of subjects with either a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40 or a prevaccination HAI titer ≥1:10 and a minimum 4-fold rise in postvaccination HAI antibody titer with respect to the prevaccination titer for influenza virus strains.

All binary endpoints including seroprotection and seroconversion rates after SIIV as well as those defined in Section 2 will be descriptively summarized with 2-sided 95% CIs for each vaccine group by the Clopper-Pearson exact method.

In addition, for seroprotection and seroconversion rates, exact, unconditional, 2-sided 95% CIs on the difference in percentages will be calculated between subjects vaccinated with SIIV concomitantly with RSV vaccine at 1 month after Vaccination 1 and subjects vaccinated with SIIV alone at 1 month after Vaccination 2 in the expanded cohort. For expanded-cohort subjects participating in the revaccination stage, seroprotection and seroconversion rates after Vaccination 3 and Vaccination 4 will be calculated in the same way. The CIs will be computed using the procedure of Chan and Zhang, using the standardized test statistic and gamma=0.000001.

Subgroup analysis for immunogenicity results may be carried out for the younger age group (18-49 years of age) by sex, provided that the numbers of subjects in the subgroups are sufficient for a meaningful data summary. Detailed specification of subgroup analysis will be included in the study SAP.

Reverse cumulative distribution curves (RCDCs) for RSV-neutralizing antibody titers for a combination of prespecified time points and vaccine groups will be generated.

Detailed analyses of all the immunogenicity endpoints, including graphical displays, will be described in the SAP.

9.3. Safety Analysis

Similar to the immunogenicity results, safety results will be analyzed separately for all the formulations in the sentinel cohort and in the expanded cohort for each age group. Within each age group in the sentinel cohort, all subjects who receive placebo will be combined as the control group.

Within each cohort, safety results will be summarized by formulation and dose level for the sentinel cohort, and summarized by formulation, dose level, and vaccination sequence for the expanded cohort.

In addition, safety results from the sentinel and the expanded cohorts will be combined and analyzed together as appropriate. For each age group at a given dose level, safety results of up to 1 month after vaccination from the subjects in the sentinel cohort will be combined with the results of up to 1 month after Vaccination 1 from the subjects in the expanded cohort who receive the same RSV vaccine formulation plus placebo at Vaccination 1. For example, in the RSV 60-μg dose level, RSV vaccine 60 μg (sentinel cohort) combines with RSV vaccine 60 μg/placebo+SIIV (expanded cohort); RSV vaccine 60 μg +$Al(OH)_3$ (sentinel cohort) combines with RSV vaccine 60 μg+$Al(OH)_3$/placebo+SIIV (expanded cohort).

All safety results following Vaccinations 3 and 4 will be summarized by formulation and vaccination sequence for the expanded-cohort subjects receiving revaccinations.

All subjects receiving a dose of at least one of the investigational products will be included in the safety population. For the safety analyses, subjects will be analyzed according to the investigational product received.

The safety endpoints are primary endpoints in the study and their analyses are based on the safety population.

The safety analyses are descriptive evaluations of local reactions, systemic events, AEs, MAEs, and SAEs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

Descriptive summary statistics (eg, counts and percentages) will be provided for AEs and e-diary events collected with 2-sided 95% exact CIs as appropriate.

The 3-tier approach will be used for the AE summary. A detailed definition for each tier will be described in the SAP.

9.4. Analysis Timing

Several analyses are planned before the final analysis at the completion of the study.

1. **Sentinel cohort, age groups 18 to 49 years and 50 to 85 years of age:**

   An analysis will be conducted when 1-month post vaccination immunogenicity data from all subjects in the sentinel cohort are available. All available safety, tolerability, and immunogenicity data will be included in the analysis.

2. **Expanded cohort, age groups 18 to 49 years of age:**

   An analysis will be conducted when 1-month post–Vaccination 1 RSV immunogenicity results from all subjects 18 to 49 years of age in the expanded cohort are available. All available safety, tolerability, and immunogenicity data will be included in the analysis. The analysis results will be used to select the most appropriate dose(s) and formulation(s) of the RSV vaccine for the Phase 2 trial for the maternal indication.

3. **Expanded cohort, age groups 18 to 49 years and 65 to 85 years of age:**

   An analysis will be conducted when 1-month post–Vaccination 2 immunogenicity results from all subjects in the expanded cohort are available. All available safety, tolerability, and immunogenicity data will be included in the analysis. The analysis results will be used to select the most appropriate dose(s) and formulation(s) of the RSV vaccine for use in pregnant women and older adults.

4. **Expanded cohort, age groups 18 to 49 years and 65 to 85 years of age:**

   An analysis will be conducted when 1-month post–Vaccination 2 influenza vaccine immunogenicity results from all subjects in the expanded cohort are available. The analysis will focus on influenza vaccine antibody immunogenicity.

CCI [redacted]

Additional analysis may be conducted before the final analysis to support other internal program level decisions as needed.

The final analysis will be performed after all of the subjects complete the study and when all of the data are available.

Safety data will be summarized on an ongoing basis. No multiplicity adjustments will be applied for these analyses.

9.5. Data Monitoring Committee(s)

This study will use an unblinded IRC and an unblinded E-DMC. The IRC will consist of at least 3 qualified Pfizer experts, including at least a physician and a statistician, who are not directly involved in the study conduct.

The IRC will conduct a 14-day safety review for each dose level in the sentinel cohort to determine if randomization in the next-higher dose should begin and if any dose level(s) should be discontinued in the expanded cohort. The IRC will also be involved in assessment of AEs that may meet stopping rule criteria.

The E-DMC will review study data as detailed in the charter and any time a stopping rule is met or other safety concern is identified. The E-DMC will also review study data at the following time points:

- When the safety data analysis(es) through 1 month after vaccination for the sentinel cohort is available.
- When the immunogenicity data analysis(es) through 1 month after vaccination for the sentinel cohort is available.
- When the safety data analysis(es) through 1 month after Vaccination 2 for the expanded cohort is available.
- When the immunogenicity data analysis(es) through 1 month after Vaccination 2 for the expanded cohort is available.
- When the safety data analysis(es) through 1 month after Vaccination 4 for the expanded-cohort revaccination stage is available.
- When the immunogenicity data analysis(es) through 1 month after Vaccination 4 for the expanded-cohort revaccination stage is available.
- When the data analysis through the last study visit is available.

The E-DMC will not participate in the dose-escalation decision.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decisions. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed ICDs, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The ICDs and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The ICDs used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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 investigational product, 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of the RSV vaccine at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a reasonable time frame. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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 US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

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

Abbreviation	Term
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CK	creatine kinase
COPD	chronic obstructive pulmonary disease
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
dLIA	direct-binding Luminex immunoassay
EC	ethics committee
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FI-RSV	formalin-inactivated RSV vaccine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
Hb	hemoglobin
HBc Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HD	high-dose
HIV	human immunodeficiency virus
HRSV	human respiratory syncytial virus
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product

Abbreviation	Term
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
LFT	liver function test
LRTI	lower respiratory tract infection
LSLV	last subject last visit
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NaCL	sodium chloride
NHP	nonhuman primate
PCD	primary completion date
PCR	polymerase chain reaction
PI	principal investigator
PT	prothrombin time
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SIIV	seasonal inactivated influenza vaccine
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TdaP	tetanus, diphtheria, and acellular pertussis vaccine
ULN	upper limit of normal
US	United States

Appendix 2. Country-Specific Requirements: Applies to South Africa Only

In addition to the individual criteria included in exclusion criterion 5 in Section 4.2, a human immunodeficiency virus (HIV) test is also required:

5. Known infections with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV). (Subjects must have a negative test for HIV at Visit 1 before vaccination.)

In Section 6.10 Expanded Cohort, Visit 1: Vaccination 1 (Day 1), the following procedure will be added:

- HIV rapid test to confirm eligibility before vaccination. If the HIV rapid test result is positive, the subject will be excluded from participation in the study.

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Signed By:	Date(GMT)	Signing Capacity
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