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

| | |
|---|---|
| Investigational Product Number: | PF-06928316 |
| Investigational Product Name: | Respiratory Syncytial Virus (RSV) Vaccine |
| United States (US) Investigational New Drug (IND) Number: | CCI [redacted] |
| European Clinical Trials Database (EudraCT) Number: | Not Applicable (N/A) |
| Protocol Number: | C3671002 |
| Phase: | 1/2 |

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

## Document History

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Protocol Amendment 3 | 22 August 2019 | Document History: Added Summary of Changes for Amendment 3. Removed hyperlinks from Amendment 2 due to changes in formatting.<br><br>Protocol Summary: Added clarification text included in various sections of the main body of the protocol to match the revisions made to the protocol.<br><br>Schedule of Activities:<br><br>Table 1: Added a reference to Stage 1; changed the Visit 5 window; modified the blood volume collection for Visit 5; added the peripheral blood mononuclear cell (PBMC) abbreviation; amended the table footer. Table 2: Added a Schedule of Activities for the Primary Study Cohort - Stage 2. Table 3: Added a schedule of activities for the RSV Vaccine Month-0, Month-2 Cohort.<br><br>Introduction: Added the rational for Amendment 3.<br><br>Study Objectives And Endpoints: Added text to clarify that the existing objectives and endpoints applied to the Primary Study Cohort - Stage 1/ vaccination 1. Added objectives and endpoints for the Primary Study Cohort - Stage 2 and the RSV Vaccine Month-0, Month-2 Cohort.<br><br>Study Design: Modified the text to introduce a new design of 3 cohorts: the Primary Study Cohort - Stage 1 and Stage 2 and RSV Vaccine Month-0, Month-2 Cohort.<br><br>Section 3.1: Updated the text to reflect the subject numbers based on the new design and updated Table 4 based on the new subject numbers. Modified the table |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | footer.<br><br>Section 4: Added inclusion criterion 5. Modified exclusion criteria 4 and 5 to reflect the new design. Added exclusion criterion 14 so that elderly subjects are not compromised due to frequent blood draws.<br><br>Section 5.1.2: Modified blinding text in line with the new design.<br><br>Section 5.4.1.1 and Table 5: Replaced "TBD" with the RSV vaccine dose.<br><br>Section 5.5: Modified the vaccine administration text to describe the timing of vaccinations by cohort. Table 6: Added administration information by cohort.<br><br>Section 5.8.2: Added a statement regarding the exclusionary period for the influenza vaccine for the Stage 2 cohort.<br><br>Section 5.8.3: Added applicability text for the administration of the influenza vaccine. Added a statement on the timing of the administration of the influenza vaccine for the RSV Month-0, Month-2 Cohort.<br><br>Section 6: Added text to note that Section 6.1 applies to the Primary Study Cohort - Stage 1. Added text to emphasize that blood samples for cellular assays apply to consenting PBMC subjects at PBMC collection sites only.<br><br>Section 6.2: Added a detailed visit schedule for the Primary Study Cohort - Stage 2.<br><br>Section 6.3: Added a detailed visit schedule for the RSV Vaccine Month-0, |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | Month-2 Cohort.<br><br>Section 7.2: Modified the immunogenicity blood sample collection to reflect sampling by study cohort.<br><br>Section 7.3: Moved the text into a logical order based on the new design. Made slight modifications to text based on the new design.<br><br>Section 8.1.4: Clarified the text to emphasize the adverse event (AE) collection periods based on the modified vaccination schedules.<br><br>Section 9: Modified the sample size determination by study cohort. Modified the probability table based on the new subject numbers per cohort.<br><br>Section 9.2: Modified study populations to reflect the new design.<br><br>Section 9.4: Modified text to show that 3 interim analyses will be performed. Text includes timing relative to vaccination and data to be analyzed.<br><br>Section 9.5: Removed redundant text regarding the timing of the data monitoring committee (DMC) review as details are addressed in the DMC charter.<br><br>Throughout: Made minor editorial revisions as appropriate. |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Protocol Amendment 2 | 09 October 2018 | Protocol Summary: Added clarification text included in various sections of the main body of the protocol to streamline the revisions made to the protocol.<br><br>Schedule of Activities: Deleted the sentinel-cohort table, the expanded cohort text within the table title, and the 2-month follow-up visit column; clarified the study assessments at scheduled visits for all subjects; added a subset of subjects at designated sites only, having whole blood samples collected at Visits 1, 2 (1-week and 1-month follow-up visits), and 4; added a Visit 2 (1-week follow-up visit) for the subset of subjects only. Changes made in line with revisions to the study design and assessment visits.<br><br>Section 1.2 and Section 2: Added preliminary safety information from the C3671001 first-in-human study; added clarification regarding the rationale for this amendment and the revised study objectives and endpoints.<br><br>Section 3 and Section 5: Added clarification text to describe the changes to the study design, investigational product, and administration requirements for the study.<br><br>Section 4: Revised the inclusion and exclusion criteria text in line with study design changes and reorganized the criteria to address inconsistencies.<br><br>Section 6.1 through Section 6.10: Deleted assessment visits, including text specific to the sentinel cohort. Deleted text specific to the expanded cohort, but revised text to address the changes to the schedule of assessments and associated procedures. Revisions made in line with the revised study objectives and |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | endpoints.<br><br>Section 7.1, Section 7.2, and Section 7.2.2: Added clarification text pertaining to the whole blood sampling procedures for the subset of subjects. New study assessment.<br><br>Section 7.1.1 through Section 7.1.3: Deleted text for laboratory assessments previously associated with the sentinel cohort, as this is no longer applicable to the study.<br><br>Section 7.3: Added safety text pertaining to the slow subject recruitment strategy during the first week of enrollment in the study, to maintain safety oversight.<br><br>Section 7.4: Revised stopping rule text for the current amendment. Revisions made in line with the changes to the study design and investigational product.<br><br>Section 8.1.4: Clarified the reporting requirements for adverse events and serious adverse events in the study.<br><br>Section 8.4.2: Clarified the reporting procedures for adverse events of specific interest.<br><br>Section 8.5: Clarified the medical device reporting requirements for the study.<br><br>Section 9: Added text to clarify the statistical analysis procedures in line with the current revisions.<br><br>Section 9.5: Deleted text regarding the IRC review process and dose escalation, as this is no longer applicable, as the sentinel cohort is no longer applicable to the study.<br><br>Appendix 2: Deleted the country-specific |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | criteria for South Africa only.<br><br>Throughout: Several changes were made to this protocol amendment to incorporate the subset of subjects that will be providing whole blood samples for the exploratory objectives as part of the new study assessment.<br><br>Throughout: Made minor editorial revisions as appropriate. |
| Protocol Amendment 1 | 18 June 2018 | Schedule of Activities (footnote b) and Section 3, Section 6.2, and Section 7.3: Added text to describe ≥4-hour observation of the first 4 subjects in the study age group of interest, vaccinated at the first site only, as requested by the central institutional review board (IRB).<br><br>Section 3: Revised text to clarify the randomization process in the sentinel and expanded cohorts.<br><br>Section 4.2: Expanded the exclusion criterion "History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product(s)" to include "or history of severe allergic reaction (eg, anaphylaxis) to any substance," for safety reasons.<br><br>Section 4.2, Section 5.8.2, and Section 5.8.3: Added inhaled/nebulized and topical epidural corticosteroids to the list of permitted corticosteroids, to address inconsistency with Section 4.3.<br><br>Section 5.1.2: Clarified that the personnel not directly involved in the study will review safety data (ie, rather than unblinded), according to an internal review committee (IRC) charter.<br><br>Section 5.4: Amended section title from |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | "Vaccine Supplies" to "Investigational Product Supplies."<br><br>Section 6.1 and Section 6.10: Added text to address the exception granted to Vaccines by the Global Standards Board to collect the subjects' full date of birth.<br><br>Section 7.4.1: Clarified that meeting a stopping rule will halt randomization and not enrollment.<br><br>Section 9.5: Clarified that review by the IRC will determine if randomization in the next higher dose level should begin.<br><br>Appendix 2: Added the appendix to provide country-specific criteria for South Africa only.<br><br>Throughout: Made minor editorial revisions as appropriate. |
| Original protocol | 05 December 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), as well as information provided in any protocol administrative change letter(s).

## TABLE OF CONTENTS

## LIST OF TABLES

## APPENDICES

## PROTOCOL SUMMARY

### Indication

The respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSV vaccine) is being developed for the following indication:

- 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: |
|---|---|
| **Primary Study Cohort - Stage 1**<br><br>To describe the safety and tolerability of an adjuvanted RSV vaccine given concomitantly with seasonal inactivated influenza vaccine (SIIV). | **Primary Study Cohort - Stage 1**<br><br>• Local reactions within 14 days after Vaccination 1.<br>• Systemic events within 14 days after Vaccination 1.<br>• Adverse events (AEs) within 1 month after Vaccination 1.<br>• Medically attended AEs and serious adverse events (SAEs) through 12 months after Vaccination 1 (from Visit 1 through Visit 5). |

### Study Design

This is a Phase 1/2, multicenter, randomized, placebo-controlled, observer-blind, dose-and formulation-finding study to describe the safety, tolerability, and immunogenicity of up to 7 different RSV vaccine candidates with bivalent formulations (RSV A and RSV B) at 3 dose levels of 60 µg of the prefusion RSV F antigens CCI [redacted] 120 µg (CCI [redacted] and 240 µg CCI [redacted] formulated with aluminum hydroxide ($Al[OH]_3$) or $CpG/Al(OH)_3$, or a 240 µg RSV vaccine CCI [redacted] alone, when administered concomitantly with SIIV, or without SIIV in a Month-0, Month-2 schedule.

The dose for the RSV vaccine alone was selected based on 1-month postvaccination immunogenicity data from the sentinel-cohort subjects in Study C3671001 (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; ClinicalTrials.gov identifier: NCT03529773).

The C3671002 study was initiated under protocol Amendment 2 during the southern hemisphere influenza season; however, a delay in SIIV availability prevented completion of enrollment of the original cohort. Consequently, only 250 subjects of the planned 312 subjects were enrolled. In Amendment 3, this cohort will be referred to as the Primary Study Cohort - Stage 1.

Enrollment in the Primary Study Cohort - Stage 1 commenced in April 2019 and completed enrollment in June 2019.

Approximately 250 subjects 65 to 85 years of age received 2 intramuscular injections at Visit 1 to assess the concomitant administration of SIIV when given to subjects receiving one of the 3 RSV vaccine dose-level candidates formulated with $Al(OH)_3$ or $CpG/Al(OH)_3$ or the RSV vaccine–alone dose (see Section 6.1 for further details).

The first 4 subjects vaccinated in the study were observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. Vaccination of the remaining subjects commenced no sooner than 48 hours after the fourth subject received his or her vaccination. Vaccination of subjects was limited to a maximum of 6 subjects per day during the first week of enrollment (up to 30 vaccinated subjects in total). Follow-up will continue through Month 12.

Protocol Amendment 3 will address 2 broad goals:

1. Evaluate a 2-dose regimen administered 2 months apart to determine whether a short dosing interval elicits an enhanced immune response.

   Due to the deficit in the originally planned subject enrollment, approximately 62 subjects aged 65-85 years will be randomized 1:1 to receive a dose of 240 µg RSV vaccine with $CpG/Al(OH)_3$ or placebo followed by a second dose 2 months later. Safety, tolerability, and immunogenicity will be evaluated. This cohort will be known as the RSV Vaccine Month-0, Month-2 Cohort. The subjects will be enrolled before the influenza season. There will be no concomitant SIIV administration.

2. Evaluate safety and immunogenicity of a second dose of RSV vaccine administered to the Primary Study Cohort - Stage 1 subjects, 12 months after the initial dose to determine whether the immune response supports annual vaccination.

   The safety and immunogenicity data from C3671001 and Stage 1 of C3671002 will guide the decision on whether a second dose of the RSV vaccine will be evaluated in Stage 2. If Stage 2 proceeds, this cohort will be known as the Primary Study Cohort - Stage 2. If there are no substantial differences in immune responses between the $CpG/Al(OH)_3$ and $Al(OH)_3$ formulations, then development of the $CpG/Al(OH)_3$ formulation may cease, and Stage 2 will not proceed.

If the data support implementation of Stage 2, invited, consenting subjects will be revaccinated with the same dose and formulation of the RSV vaccine or placebo received at Visit 1, concomitantly with SIIV. The safety, tolerability, and immunogenicity of the second dose will be evaluated through 12 months after revaccination.

**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 within 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 and nonchildbearing-potential female adults 65 to 85 years of age at the time of enrollment (signing of the ICD).

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

   - 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;

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   - Have medically confirmed ovarian failure.

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

5. Subjects must have received the primary vaccination (RSV vaccine or placebo) at Visit 1 and have signed and dated the ICD for participating in the revaccination stage (applies to Primary Study Cohort - Stage 2 subjects).

**Exclusion Criteria**

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

1. 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.

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

3. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

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

5. Vaccination with any influenza vaccine within 6 months (182 days) before investigational product administration (applies to Primary Study Cohort - Stages 1 and 2).

6. 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, a history of severe allergic reaction (eg, anaphylaxis) to any substance, including documented allergy to egg proteins (egg or egg products) or chicken proteins.

7. Subjects with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

8. Subjects receiving 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 (epidural, skin, or eyes) corticosteroids are permitted.

9. Subjects 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 syndrome, idiopathic thrombocytopenic purpura, autoimmune glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

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

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

12. Female subjects of childbearing potential or who are pregnant or breastfeeding; fertile male subjects who are unwilling to use a highly effective method of contraception for at least 28 days after the last dose of investigational product.

13. 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.

14. Planned donation of blood volumes of approximately 470 mL within 12 weeks after Vaccination 1 (applies to subjects having additional blood drawn for cellular assays).

**Investigational Products**

**Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine**

CCI [redacted]

There are 3 different presentations of RSV drug product. The $Al(OH)_3$- and $CpG/Al(OH)_3$-containing formulations consist of 3 different dose levels of lyophilized RSV antigen (60 µg, 120 µg, and 240 µg). The RSV antigens without $Al(OH)_3$ or $CpG/Al(OH)_3$ will consist of a single dose level (240 µg). The lyophilized cake is reconstituted with one of 3 diluents: a sterile suspension of $Al(OH)_3$ in water for injection, a sterile suspension of $CpG/Al(OH)_3$, or sterile water for injection.

**Seasonal Inactivated Influenza Vaccine**

Commercially available high-dose (HD) trivalent SIIV (if available) or quadrivalent SIIV will be administered to the Primary Study Cohort - Stages 1 and 2.

Investigational sites will be notified which commercially available SIIV will be provided prior to the start of enrollment.

**Placebo**

The placebo 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 any formal statistical hypothesis testing. Statistical analysis will be descriptive in nature.

The safety analyses include local reactions, systemic events, AEs, medically attended AEs (MAEs), AEs of specific interest, and SAEs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The counts and percentages will be provided for AEs and e-diary events, with 2-sided 95% exact CIs as appropriate.

For immunogenicity endpoints, geometric mean titer (GMT) and geometric mean fold rise (GMFR) from baseline will be calculated by vaccine group and by cohort along with the 95% confidence intervals. Relevant comparisons between vaccine groups and by cohorts will be based on the ratios of postvaccination GMTs, and the associated 2-sided 95% confidence intervals will also be constructed.

The percentages of subjects achieving seroprotection and seroconversion at 1 month after vaccination will be computed for each virus strain contained in SIIV separately.

**Interim Analyses**

Three interim analyses outlined in Section 9.4 are planned before the final analysis at the completion of the study. The results of these analyses will be used to select the most appropriate dose(s), formulation(s), and dosing schedule of the RSV vaccine for use in further studies.

## 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.

Table 1 Schedule of Activities applies to those subjects participating in the Primary Study Cohort - Stage 1 (single dose administration of RSV vaccine/placebo given concomitantly with SIIV). Study procedures for this cohort are fully described in Section 6.1.

**Table 1. Schedule of Activities: Primary Study Cohort - Stage 1**

| **Visit Number** | **1** | **2** [a] | **2** | **3** | **4** | **5** [b] |
|---|---|---|---|---|---|---|
| **Visit Description** | **Vaccination** | **1-Week Follow-up Visit** | **1-Month Follow-up Visit** | **3-Month Follow-up Visit** | **6-Month Follow-up Visit** | **12-Month Follow-up Visit** |
| **Study Period** | **Month 0** | | **Month 1** | **Month 3** | **Month 6** | **Month 12** |
| **Visit Window (Days)** | **Day 1** | **6 to 8 Days After Visit 1** | **28 to 35 Days After Visit 1** | **84 to 105 Days After Visit 1** | **168 to 210 Days After Visit 1** | **300 to 400 Days After Visit 1** |
| Obtain informed consent | X | | | | | |
| Assign subject number | X | | | | | |
| Obtain demography and medical history data | X | | | | | |
| Assess tobacco usage | X | | | | | |
| Document medications currently taken | X | | | | | |
| Perform physical examination, including vital signs (weight, height, oral temperature, heart rate, and seated blood pressure) | X | | | | | |
| Collect nonstudy vaccine information | X | X | X | X | X | X |
| Confirm eligibility | X | | | | | |
| Review temporary delay criteria | X | | | | | |
| Confirm understanding of and compliance with protocol requirements for contraception (male subjects only) | X | X | X | | | |

**Table 1. Schedule of Activities: Primary Study Cohort - Stage 1**

| **Visit Number** | **1** | **2** [a] | **2** | **3** | **4** | **5** [b] |
|---|---|---|---|---|---|---|
| **Visit Description** | **Vaccination** | **1-Week Follow-up Visit** | **1-Month Follow-up Visit** | **3-Month Follow-up Visit** | **6-Month Follow-up Visit** | **12-Month Follow-up Visit** |
| **Study Period** | **Month 0** | | **Month 1** | **Month 3** | **Month 6** | **Month 12** |
| **Visit Window (Days)** | **Day 1** | **6 to 8 Days After Visit 1** | **28 to 35 Days After Visit 1** | **84 to 105 Days After Visit 1** | **168 to 210 Days After Visit 1** | **300 to 400 Days After Visit 1** |
| Assign randomization number | X | | | | | |
| Collect blood sample for antibody assessment | ~50 mL | ~50 mL | ~50 mL | ~50 mL | ~50 mL | ~25 mL |
| Collect blood sample for cellular assay [c] | **~100 mL** | **~50 mL** | **~50 mL** | | **~50 mL** | |
| Administer investigational product and SIIV in opposite arms | X | | | | | |
| Assess acute reactions for at least 30 minutes after investigational product administration | 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, AEs of specific interest, and SAEs as appropriate | X | X | X | X | X | X |

Abbreviations: e-diary = electronic diary; SIIV = seasonal inactivated influenza vaccine; PBMC = peripheral blood mononuclear cell.

a. This visit is only applicable to subjects consenting to PBMC collection at designated PBMC sites.
b. This Visit 5 schedule applies only to subjects who are not invited or do not consent to revaccination at Month 12.
c. This blood collection is only applicable to subjects consenting to PBMC collection at designated PBMC sites.

Table 2 Primary Study Cohort - Stage 2 Schedule of Activities is applicable to Stage 1 subjects who are invited and consent to revaccination at Month 12. Study procedures for this cohort are fully described in Section 6.2.

**Table 2. Schedule of Activities: Primary Study Cohort - Stage 2**

| **Visit Number** | **5** [a] | **6A** [b] | **6** | **7** | **8** | **9** |
|---|---|---|---|---|---|---|
| **Visit Description** | **Vaccination 2** | **1-Week Revaccination Follow-up Visit** | **1-Month Revaccination Follow-up Visit** | **3-Month Revaccination Follow-up Visit** | **6-Month Revaccination Follow-up Visit** | **12-Month Revaccination Follow-up Visit** |
| **Study Period** | **Month 12** | | **Month 13** | **Month 15** | **Month 18** | **Month 24** |
| **Visit Window (Days)** | **300 to 400 Days after Visit 1** | **6 to 8 Days After Visit 5** | **28 to 35 Days After Visit 5** | **84 to 105 Days After Visit 5** | **168 to 210 Days After Visit 5** | **350 to 378 Days After Visit 5** |
| Confirm/obtain informed consent for Stage 2 [c] | X | | | | | |
| Perform physical examination, vital signs (weight, oral temperature, heart rate, and seated blood pressure) | X | | | | | |
| Review inclusion/exclusion criteria | X | | | | | |
| Record nonstudy vaccine information | X | X | X | X | X | X |
| Review temporary delay criteria | X | | | | | |
| Confirm understanding and compliance with protocol requirements for contraception (male subjects) | X | X | X | | | |
| Obtain IP container number | X | | | | | |
| Collect blood sample for antibody assessment | ~25 mL | | ~25 mL | ~25 mL | ~25 mL | ~25 mL |
| Collect blood sample for cellular assay [d] | **~100 mL** | **~50 mL** | **~50 mL** | | **~50 mL** | |
| Administer investigational product in left deltoid muscle and SIIV in right deltoid muscle | X | | | | | |
| Assess acute reactions for at least 30 minutes after investigational product administration | X | | | | | |
| Provide subject with 14-day e-diary, thermometer, and measuring device | X | | | | | |
| Review e-diary data (daily review is optimal | ----------X---------- | | | | | |

**Table 2. Schedule of Activities: Primary Study Cohort - Stage 2**

| **Visit Number** | **5** [a] | **6A** [b] | **6** | **7** | **8** | **9** |
|---|---|---|---|---|---|---|
| **Visit Description** | **Vaccination 2** | **1-Week Revaccination Follow-up Visit** | **1-Month Revaccination Follow-up Visit** | **3-Month Revaccination Follow-up Visit** | **6-Month Revaccination Follow-up Visit** | **12-Month Revaccination Follow-up Visit** |
| **Study Period** | **Month 12** | | **Month 13** | **Month 15** | **Month 18** | **Month 24** |
| **Visit Window (Days)** | **300 to 400 Days after Visit 1** | **6 to 8 Days After Visit 5** | **28 to 35 Days After Visit 5** | **84 to 105 Days After Visit 5** | **168 to 210 Days After Visit 5** | **350 to 378 Days After Visit 5** |
| during the active diary period) | 14 days | | | | | |
| Review and collect e-diary | | | X | | | |
| Record AEs, medically attended AEs, AEs of specific interest, and SAEs as appropriate | X | X | X | X | X | X |

Abbreviations: e-diary = electronic diary; SIIV = seasonal inactivated influenza vaccine; PBMC = peripheral blood mononuclear cell.

a. This Visit 5 schedule applies to subjects invited and consenting to revaccination at Month 12.
b. Visit 6A is only applicable to subjects consenting to PBMC collection at designated PBMC sites.
c. Consent may be obtained prior to Visit 5.
d. This blood collection is only applicable subjects consenting to PBMC collection at designated PBMC sites.

Table 3 Schedule of Activities is applicable to subjects participating in the RSV Vaccine Month-0, Month-2 Cohort. Study procedures for this cohort are fully described in Section 6.3.

**Table 3. Schedule of Activities: RSV Vaccine Month-0, Month-2 Cohort**

| **Visit Number** | **1** | **2A** [a] | **2** | **3** | **4A** [a] | **4** | **5** | **6** |
|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Vaccination 1** | **1-Week Post-Vaccination 1 Follow-up Visit** | **1-Month Post-Vaccination 1 Follow-up Visit** | **Vaccination 2** | **1-Week Post-Vaccination 2 Visit** | **1-Month Post-Vaccination 2 Visit** | **6-Month Post-Vaccination 2 Visit** | **12-Month Post-Vaccination 2 Visit** |
| **Study Period** | **Month 0** | | **Month 1** | **Month 2** | | **Month 3** | **Month 8** | **Month 14** |
| **Visit Window (Days)** | **Day 1** | **6 to 8 Days After Visit 1** | **28 to 35 Days After Visit 1** | **54 to 66 Days After Visit 1** | **6 to 8 Days After Visit 3** | **28 to 35 Days After Visit 3** | **168 to 210 Days After Visit 3** | **350 to 378 Days After Visit 3** |
| Obtain informed consent | X | | | | | | | |
| Assign subject number | X | | | | | | | |
| Obtain demography and medical history data | X | | | | | | | |
| Assess tobacco usage | X | | | | | | | |
| Document medications currently taken | X | | | | | | | |
| Perform physical examination, including vital signs (weight, height, oral temperature, heart rate, and seated blood pressure) | X | | | | | | | |
| Record nonstudy vaccine information | X | X | X | X | X | X | X | X |
| Confirm eligibility | X | | | | | | | |
| Review temporary delay criteria | X | | | X | | | | |
| Confirm understanding of and compliance with protocol requirements for contraception (male subjects only) | X | X | X | X | X | X | | |
| Assign randomization number | X | | | | | | | |
| Collect blood sample for antibody | ~25 mL | | ~25 mL | ~25 mL | | ~25 mL | ~25 mL | ~25 mL |

## Table 3. Schedule of Activities: RSV Vaccine Month-0, Month-2 Cohort

| **Visit Number** | **1** | **2A [a]** | **2** | **3** | **4A [a]** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Vaccination 1** | **1-Week Post-Vaccination 1 Follow-up Visit** | **1-Month Post-Vaccination 1 Follow-up Visit** | **Vaccination 2** | **1-Week Post-Vaccination 2 Visit** | **1-Month Post-Vaccination 2 Visit** | **6-Month Post-Vaccination 2 Visit** | **12-Month Post-Vaccination 2 Visit** |
| **Study Period** | **Month 0** | | **Month 1** | **Month 2** | | **Month 3** | **Month 8** | **Month 14** |
| **Visit Window (Days)** | **Day 1** | **6 to 8 Days After Visit 1** | **28 to 35 Days After Visit 1** | **54 to 66 Days After Visit 1** | **6 to 8 Days After Visit 3** | **28 to 35 Days After Visit 3** | **168 to 210 Days After Visit 3** | **350 to 378 Days After Visit 3** |
| assessment | | | | | | | | |
| Collect blood sample for cellular assay [b] | ~100 mL | ~50 mL | ~50 mL | ~50 mL | ~50 mL | ~50 mL | ~50 mL | ~50 mL |
| Administer investigational product in the LEFT deltoid muscle | 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 | | | X | | | | |
| Review e-diary data (daily review is optimal during the active diary period) | ----------X---------- 14 days | | | ----------X---------- 14 days | | | | |
| Review and collect e-diary | | | X | | | X | | |
| Record AEs, medically attended AEs, AEs of specific interest, and SAEs as appropriate | X | X | X | X | X | X | X | X |

Abbreviations: e-diary = electronic diary; PBMC = peripheral blood mononuclear cell.

a. Visit is only applicable to subjects consenting to PBMC collection at designated PBMC sites.
b. This blood collection is only applicable subjects consenting to PBMC collection at designated PBMC sites.

# 1. INTRODUCTION

## 1.1. Indication

The respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSV vaccine) is being developed for the following indication:

- 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. HRSV exists as 2 antigenic subgroups, A and B, which exhibit genome-wide 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 in children younger than 5 years, which resulted in about 3.2 million hospital admissions and about 59,600 hospital deaths. 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 LRTI.[2]

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.[5,6]

The antibody is costly, requires multiple monthly injections, and is recommended for use only in high-risk and premature infants.[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, in order to protect infants by maternal immunization during pregnancy, and adults 60 years of age and older via direct immunization.

The aim of RSV vaccination 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] Serum neutralizing antibody titers in RSV-infected patients who were hospitalized compared with nonhospitalized infected persons suggest that more severe RSV disease is associated with low serum neutralizing antibody.[7] 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]

Because immunosenescence[8] could pose a barrier to effective immunization of the elderly against RSV, there is concern that despite findings in animals suggesting that $Al(OH)_3$ improves the immune response to the vaccine, the addition of $Al(OH)_3$ alone may not be sufficient to optimize responses in the elderly, who are at significant risk from RSV disease.

In this study in older adults 65 to 85 years of age, a CpG with aluminum hydroxide ($CpG/Al[OH]_3$)-adjuvanted formulation, given as a single dose or in a 2-dose regimen administered 2 months apart, will be investigated to assess if the addition of CpG could further improve neutralizing antibody levels relative to formulations with or without $Al(OH)_3$ at the same dose levels used in the FIH study. In this event, a $CpG/Al(OH)_3$-adjuvanted formulation would be included in further development studies. CpG is a Toll-like receptor 9 (TLR9) agonist that has been generally well tolerated in human clinical trials for infectious disease indications, such as hepatitis B, malaria, and influenza.[9] A CpG-containing hepatitis B vaccine, Heplisav-B, was recently licensed in the United States.[10] CCI [redacted] Additionally, it is anticipated that an RSV vaccine would optimally be given at the same time as a seasonal influenza vaccine, to facilitate its use in the older adult population. Therefore, this study will assess any potential impact on safety, tolerability, and immune responses to the seasonal inactivated influenza vaccine (SIIV) when the RSV vaccine and SIIV are given concomitantly; similar assessments of concomitant administration of influenza vaccine and RSV vaccine with or without $Al(OH)_3$ are being conducted in the C3671001 study.

Data from the C3671001 study at 1 month after administration of the 3 dose levels of RSV vaccine (60 µg, 120 µg, and 240 µg), with or without $Al(OH)_3$ in subjects aged 18 to 85 years, have shown the vaccine is well tolerated and immunogenic, with a trend toward greater immunogenicity at the 240-µg dose level.

The C3671002 study was initiated under protocol Amendment 2 during the southern hemisphere influenza season; however, a delay in SIIV availability prevented the completion of enrollment of the original cohort. Consequently, only 250 subjects of the planned 312 subjects were enrolled. In Amendment 3, this cohort will be referred to as the Primary Study Cohort - Stage 1.

Protocol Amendment 3 will address 2 broad goals:

1. Evaluate a 2-dose regimen administered 2 months apart to determine whether a short dosing interval elicits an enhanced immune response.

   Due to the deficit in the originally planned subject enrollment, approximately 62 subjects aged 65-85 years will be randomized 1:1 to receive a dose of 240 µg RSV vaccine with $CpG/Al(OH)_3$ or placebo followed by a second dose 2 months later. Safety, tolerability, and immunogenicity will be evaluated. This cohort will be known as the RSV Vaccine Month-0, Month-2 Cohort. The subjects will be enrolled before the influenza season. There will be no concomitant SIIV administration.

2. Evaluate safety and immunogenicity of a second dose of RSV vaccine administered to the Primary Study Cohort - Stage 1 subjects, 12 months after the initial dose to determine whether the immune response supports annual vaccination.

The safety and immunogenicity data from C3671001 and Stage 1 of C3671002 will guide the decision on whether a second dose of the RSV vaccine will be evaluated in Stage 2. If Stage 2 proceeds, this cohort will be known as the Primary Study Cohort - Stage 2. If there are no substantial differences in immune responses between the CpG/$Al(OH)_3$ and $Al(OH)_3$ formulations, then development of the CpG/Al(OH)3 formulation may cease, and Stage 2 will not proceed.

If the data support implementation of Stage 2, invited, consenting subjects will be revaccinated with the same dose and formulation of the RSV vaccine or placebo received at Visit 1, concomitantly with SIIV. The safety, tolerability, and immunogenicity of the second dose will be evaluated through 12 months after revaccination.

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: |
|---|---|
| **Primary Study Cohort - Stage 1:**<br><br>To describe the safety and tolerability of an adjuvanted RSV vaccine given concomitantly with SIIV. | **Primary Study Cohort - Stage 1:**<br><br>• Local reactions within 14 days after Vaccination 1.<br>• Systemic events within 14 days after Vaccination 1.<br>• Adverse events (AEs) within 1 month after Vaccination 1.<br>• Medically attended AEs and serious adverse events (SAEs) through 12 months after Vaccination 1 (from Visit 1 through Visit 5). |
| **Secondary Objectives:** | **Secondary Endpoints:** |
| **Primary Study Cohort - Stage 1:**<br><br>To describe the immune responses elicited by an adjuvanted RSV vaccine given with SIIV.<br>To describe the immune responses elicited by SIIV given alone or with an adjuvanted or unadjuvanted RSV vaccine. | **Primary Study Cohort - Stage 1:**<br><br>• RSV A– and RSV B–neutralizing antibody titers measured before and 1 month after Vaccination 1.<br><br>• Hemagglutination inhibition assay (HAI) titers for all strains in the SIIV measured before and 1 month after Vaccination 1. |
| **Exploratory Objectives:** | **Exploratory Endpoints:** |
| **Primary Study Cohort - Stage 1:**<br><br>To more fully characterize the immune response to an adjuvanted RSV vaccine and to any concurrent RSV infection.<br><br>To more fully characterize the immune response to SIIV. | **Primary Study Cohort - Stage 1:**<br><br>• RSV A– and RSV B–neutralizing antibody titers measured at 1 week (peripheral blood mononuclear cell [PBMC] subjects) and 3, 6, and 12 months after Vaccination 1.<br>• Plasmablast frequencies and T-cell phenotype and functional analysis before and 1 week after Vaccination 1 (PBMC subjects).<br>• Memory B-cell and T-cell frequencies and their functional analysis before vaccination, and 1 and 6 months after Vaccination 1.<br>• Immunoglobulin G (IgG) titers against prefusion F before vaccination, and 1, 3, 6, and 12 months after Vaccination 1.<br>• IgG titers to nonvaccine RSV antigens before vaccination, and 1, 3, 6, and 12 months after Vaccination 1.<br>• H3N2-neutralizing antibody titers measured before vaccination and 1 month after Vaccination 1. |

| | |
|---|---|
| **Primary Study Cohort - Stage 2:**<br><br>To describe the safety and tolerability of a second dose of adjuvanted RSV vaccine given concomitantly with SIIV.<br><br>To describe the immune responses elicited by a second dose of an adjuvanted RSV vaccine given concomitantly with SIIV.<br><br>To more fully characterize the immune response to SIIV when given concomitantly with a second dose of RSV. | **Primary Study Cohort - Stage 2:**<br>• Local reactions within 14 days after Vaccination 2.<br>• Systemic events within 14 days after Vaccination 2.<br>• AEs within 1 month after Vaccination 2.<br>• Medically attended AEs and SAEs through 12 months after Vaccination 2.<br>• RSV A– and RSV B–neutralizing antibody titers measured at 1 week (PBMC subjects) and 1, 3, 6, and 12 months after Vaccination 2.<br>• Plasmablast frequencies and T-cell phenotype and functional analysis before Vaccination 2 and 1 week after Vaccination 2 (PBMC subjects).<br>• Memory B-cell and T-cell frequencies and their functional analysis before Vaccination 2, and 1 and 6 months after Vaccination 2.<br>• IgG titers against prefusion F before Vaccination 2, and 1, 3, 6, and 12 months after Vaccination 2.<br>• IgG titers to nonvaccine RSV antigens before Vaccination 2, and 1, 3, 6, and 12 months after Vaccination 2.<br>• HAI titers for all strains in the SIIV measured before and 1 month after Vaccination 2.<br>• H3N2-neutralizing antibody titers measured before Vaccination 2 and 1 month after Vaccination 2. |
| **RSV Vaccine Month-0, Month-2 Cohort**<br><br>To describe the safety and tolerability of the first and second dose of an adjuvanted RSV vaccine administered 2 months apart.<br><br>To describe the immune responses elicited by the first and second dose of adjuvanted RSV vaccine administered 2 months apart. | **RSV Vaccine Month-0, Month-2 Cohort**<br><br>• Local reactions within 14 days after Vaccinations 1 and 2.<br>• Systemic events within 14 days after Vaccinations 1 and 2.<br>• AEs within 1 month after Vaccinations 1 and 2.<br>• AEs from Vaccination 1 through 1 month after Vaccination 2.<br>• Medically attended AEs and SAEs through 12 months after Vaccination 2.<br>• RSV A– and RSV B–neutralizing antibody titers measured at scheduled timepoints before and after each vaccination scheduled.<br>• Plasmablast frequencies and T-cell phenotype and functional analysis before each vaccination and 1 week after Vaccinations 1 and 2 (PBMC subjects).<br>• Memory B-cell and T-cell frequencies and their functional analysis before each vaccination, and 1 and 6 months after Vaccinations 1 and 2.<br>• IgG titers against prefusion F at scheduled timepoints before and after each vaccination.<br>• IgG titers to nonvaccine RSV antigens at scheduled timepoints before and after each vaccination. |

## 3. STUDY DESIGN

This is a Phase 1/2, multicenter, randomized, placebo-controlled, observer-blind, dose- and formulation-finding study to describe the safety, tolerability, and immunogenicity of up to 7 different RSV vaccine candidates with bivalent formulations (RSV A and RSV B) at 3 dose levels of 60 µg of the prefusion RSV F antigens CCI [redacted] 120 µg CCI [redacted] and 240 µg CCI [redacted] formulated with aluminum hydroxide ($Al[OH]_3$) or $CpG/Al(OH)_3$, or a 240 µg RSV vaccine CCI [redacted] alone, when administered concomitantly with SIIV, or without SIIV in a Month-0 and Month-2 schedule.

The dose for the RSV vaccine alone was selected based on 1-month postvaccination immunogenicity data from the sentinel-cohort subjects in Study C3671001 (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; ClinicalTrials.gov identifier: NCT03529773).

The study is organized in the following cohorts:

1. Primary Study Cohort - Stage 1, will evaluate RSV vaccine doses/formulations given concomitantly with SIIV at Month 0.

2. Primary Study Cohort - Stage 2, will evaluate revaccination of the Stage 1 subjects with a RSV vaccine and concomitant SIIV, administered at Month 12.

3. RSV Vaccine Month-0, Month-2 Cohort will evaluate a 240 µg dose of RSV vaccine with $CpG/Al(OH)_3$ given at Months 0 and 2. No concomitant SIIV will be given.

Male and female subjects 65 to 85 years of age will be enrolled. Subjects will be randomized equally across all dose groups in the primary cohorts. The RSV Vaccine Month-0, Month-2 Cohort will be randomized 1:1 to receive RSV vaccine or placebo.

### Primary Study Cohort - Stage 1

Enrollment in the Primary Study Cohort - Stage 1 commenced in April 2019 and completed enrollment in June 2019. Approximately 250 subjects 65 to 85 years of age received 2 intramuscular injections at Visit 1 to assess the concomitant administration of SIIV when given to subjects receiving one of the 3 RSV vaccine dose-level candidates formulated with $Al(OH)_3$ or $CpG/Al(OH)_3$ or the RSV vaccine–alone dose (see Section 6.1 for further details).

The first 4 subjects vaccinated in the study were observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. Vaccination of the remaining subjects commenced no sooner than 48 hours after the fourth subject received his or her vaccination. Vaccination of subjects was limited to a maximum of 6 subjects per day during the first week of enrollment (up to 30 vaccinated subjects in total). Follow-up will continue through Month 12.

**Primary Study Cohort - Stage 2**

Prior to completion of Stage 1, subjects may be invited to participate in Stage 2. Safety and immunogenicity data obtained from the C3671001 and C3671002 studies will be used to determine whether Stage 2 will proceed and, if so, whether all or some of the RSV formulations will be evaluated.

If the data support implementation of Stage 2, consenting subjects will be revaccinated with the same dose and formulation of the RSV vaccine or placebo received at Visit 1, concomitantly with SIIV. The safety, tolerability, and immunogenicity of the second dose will be evaluated through 12 months after revaccination.

If the data do not support the implementation of revaccination at 12 months, Stage 2 will not proceed.

**RSV Vaccine Month-0, Month-2 Cohort**

Approximately 62 RSV vaccine-naive subjects will be randomized 1:1 to receive either 240 μg of RSV vaccine with CpG/Al(OH)$_3$ or placebo at Visit 1 (Month 0). At Visit 3 (Month 2), subjects will receive a second dose of RSV vaccine or placebo as randomized at Visit 1. No concomitant SIIV will be given.

In Stage 1, the 240-μg dose for the nonadjuvanted RSV vaccine was selected based on the 1-month postvaccination immunogenicity data from the sentinel-cohort subjects in Study C3671001. The same dose will be used for the RSV Vaccine Month-0, Month-2 Cohort.

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

## 3.1. Number of Subjects

In total, approximately 312 subjects will be randomized to receive RSV vaccine at different dose levels and formulations or placebo at different vaccination schedules. Approximately 250 subjects were enrolled in the Primary Study Cohort - Stage 1 and approximately 62 RSV vaccine-naive subjects will be enrolled in the RSV Vaccine Month-0, Month-2 Cohort (see Table 4 below). Of these, a subset of subjects in all cohorts will be included in the whole blood collection procedural requirements for the exploratory cellular analysis endpoints for this study. The subset will be determined at the site level. Those sites that have access to the appropriate specimen-processing laboratories will provide all subjects for the PBMC collection subset. It is anticipated that the subjects from the selected sites will constitute approximately 1/3 of the total number of randomized subjects.

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

## Table 4. Randomization of Subjects by Dose and Formulation

| Primary Study Cohort | | | Approximate Number of Males and Females 65 to 85 Years of Age | |
|---|---|---|---|---|
| **Dose/Formulation** | | **Stage 1 / Stage 2** | **Originally Planned Study Target** | **Vaccinated in Stage 1** |
| **60 µg** | RSV+$Al(OH)_3$ SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| | RSV+CpG/$Al(OH)_3$ SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| **120 µg** | RSV+$Al(OH)_3$ SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| | RSV+CpG/$Al(OH)_3$ SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| **240 µg** | RSV+$Al(OH)_3$ SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| | RSV+CpG/$Al(OH)_3$ SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| **240 µg** | RSV SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| | Placebo SIIV | (Month 0/Month 12 [a]) | 39 | ~31 [b] |
| | | **Total** | 312 | 250 |
| **RSV Vaccine Month-0, Month-2 Cohort** | | | **Target** | |
| **240 µg** | RSV+CpG/$Al(OH)_3$ | (Month 0/Month 2) | 31 | |
| | Placebo | (Month 0/Month 2) | 31 | |
| | | **Total** | **62** | |
| **Total study size** | | | **312** | |

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

a. Primary Study Cohort - Stage 2 is contingent on supporting data from Stage 1 and applies to invited/consenting subjects only.
b. Approximate number of subjects vaccinated in each dose/formulation group are shown, actual numbers per group will be known after unblinding.

### 3.2. Duration of Subject Participation

Subjects enrolled in the Primary Study Cohort - Stage 1 will participate in the study for approximately 12 months, or up to approximately 24 months if completing Stage 2.

Subjects enrolled in the RSV Vaccine Month-0, Month-2 Cohort will participate in the study for approximately 14 months.

### 3.3. Duration of Study

The study will last approximately 26 months.

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 the study will be conducted in the same geographic location; however, if required for operational reasons, this study may be conducted in more than 1 geographic location over more than 1 influenza season.

## 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.

### 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 within 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 and nonchildbearing-potential female adults 65 to 85 years of age at the time of enrollment (signing of the ICD).

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

- 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;
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure.

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

5. Subjects must have received the primary vaccination (RSV vaccine or placebo) at Visit 1 and have signed and dated the ICD for participating in the revaccination stage (applies to Primary Study Cohort - Stage 2 subjects).

### 4.2. Exclusion Criteria

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

1. 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.
2. Participation in other studies involving investigational product within 28 days prior to study entry and/or during study participation.
3. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
4. Previous vaccination with any licensed or investigational RSV vaccine before enrollment into the study, or planned receipt throughout the study of nonstudy RSV vaccine
5. Vaccination with any influenza vaccine within 6 months (182 days) before investigational product administration (applies to Primary Study Cohort - Stages 1 and 2).
6. 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, a history of severe allergic reaction (eg, anaphylaxis) to any substance, including documented allergy to egg proteins (egg or egg products) or chicken proteins.

7. Subjects with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

8. Subjects receiving 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 (epidural, skin, or eyes) corticosteroids are permitted.

9. Subjects 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 syndrome, idiopathic thrombocytopenic purpura, autoimmune glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

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

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

12. Female subjects of childbearing potential or who are pregnant or breastfeeding; fertile male subjects who are unwilling to use a highly effective method of contraception for at least 28 days after the last dose of investigational product.

13. 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.

14. Planned donation of blood volumes of approximately 470 mL within 12 weeks after Vaccination 1 (applies to subjects having additional blood drawn for cellular assays).

### 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.

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

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

- 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.

- 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 (epidural, skin, or eyes) corticosteroids are permitted.

### 4.4. Lifestyle Requirements

#### 4.4.1. Contraception

All fertile male subjects 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 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 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's 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:

- 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 throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness. Correctly placed intrauterine device (IUD) or hormone-releasing intrauterine system (IUS).

- 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.

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

- 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 products are RSV vaccine and placebo (saline control).

Commercially available SIIV will also be provided by the sponsor.

### 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 and placebo may differ. SIIV will be administered in an open-label fashion.

The subject, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

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, from subject randomization up until 1 month after vaccination for the Primary Study Cohort - Stage 1 and from subject randomization up until 1 month after the second vaccination for the RSV Vaccine Month-0, Month-2 Cohort, when safety and immunogenicity data are available for analysis.

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 (see Section 7.4) for details) 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

All doses of 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

Each lyophilized vial of the RSV vaccine drug product is supplied as a mixture of equal CCI

There are 3 different presentations of RSV drug product. The $Al(OH)_3$- and $CpG/Al(OH)_3$-containing formulations consist of 3 different dose levels of lyophilized RSV antigen (60 µg, 120 µg, and 240 µg). The RSV antigens without $Al(OH)_3$ or $CpG/Al(OH)_3$ will consist of a single dose level (240 µg). The lyophilized cake is reconstituted with one of 3 diluents: a sterile suspension of $Al(OH)_3$ in water for injection, a sterile suspension of $CpG/Al(OH)_3$, or sterile water for injection.

The fill volumes 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

#### 5.4.1.2. Seasonal Inactivated Influenza Vaccine

Commercially available high-dose (HD) trivalent SIIV (if available) or quadrivalent SIIV will be used in the Primary Study Cohort - Stage 1 and Stage 2.

Investigational sites will be notified which commercially available SIIV will be provided prior to the start of enrollment.

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 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. The 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.

- Primary Study Cohort - Stage 1

Subjects will receive 2 injections at Visit 1 (Day 1) in accordance with the assigned randomized treatment; see Table 6 below for administration guidance.

- Primary Study Cohort - Stage 2

Subjects will receive 2 injections at Visit 1 (Day 1) and 2 injections at Visit 5 (Month 12) in accordance with the assigned randomized treatment; see Table 6 below for administration guidance.

- RSV Vaccine Month-0, Month-2 Cohort

Subjects will receive a single injection at Visit 1 (Month 0) and at Visit 3 (Month 2) in accordance with the assigned randomized treatment; see Table 6 below for administration guidance.

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.

**Table 6. Location of Intramuscular Injection**

| Product Administered | Location of Injection |
|---|---|
| **Primary Study Cohort - Stage 1 and Stage 2** | |
| RSV+$Al(OH)_3$<br>SIIV | Left deltoid muscle<br>Right deltoid muscle |
| RSV+CpG/$Al(OH)_3$<br>SIIV | Left deltoid muscle<br>Right deltoid muscle |
| RSV<br>SIIV | Left deltoid muscle<br>Right deltoid muscle |
| Placebo<br>SIIV | Left deltoid muscle<br>Right deltoid muscle |
| **RSV Vaccine Month-0, Month-2 Cohort** | |
| RSV+CpG/$Al(OH)_3$ or placebo | Left deltoid muscle |

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 +2°C to +8°C 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 +2°C to +8°C temperature-monitored refrigerator for storage.

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products and SIIV 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.
- 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.
- Vaccination with any influenza vaccine within 6 months (182 days) before investigational product administration (applicable to Primary Study Cohort - Stage 2 subjects).
- Licensed or investigational RSV vaccines, 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 (epidural, 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

- Licensed influenza vaccine may be given during the study starting after the blood sample has been taken at the 1-month postvaccination visits (applicable to Primary Study Cohort - Stage 1 and Stage 2).

- For the RSV Vaccine Month-0, Month-2 Cohort, nonstudy licensed influenza vaccine may be given after Visit 3.
- If medically necessary (eg, pandemic), influenza vaccine may be given at any time.
- Inhaled/nebulized, intra-articular, intrabursal, or topical (epidural, 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.
- Medication other than that described as prohibited in Section 5.8.2 required for treatment of preexisting stable conditions is permitted.

### 5.8.4. Recording Nonstudy Vaccinations and Concomitant Medications

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD will be collected and recorded in the CRF. Concomitant medications will be assessed but not documented on the CRF.

## 6. STUDY PROCEDURES

### 6.1. Primary Study Cohort - Stage 1

### 6.1.1. Primary Study Cohort - Stage 1, Visit 1: Vaccination (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.
- Obtain details of any medications currently taken.

- Perform physical examination including vital signs (weight, height, oral temperature, heart rate, and seated blood pressure), 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.

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

- 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.

- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).

- Obtain the subject's randomization number and investigational product container 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.

- Prior to vaccination, collect a blood sample of approximately 100 mL for cellular assays (from consenting PBMC subjects at designated PBMC collection sites only; see Section 3.1).

- 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 SIIV into the deltoid muscle of the right arm (see Table 6). Please refer to the IP manual for further instruction on this process.

- The first 4 subjects vaccinated in the study must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For subjects enrolled thereafter, blinded site staff must observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions (including time of onset) 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.

- 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 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 (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) at the injection site on the left arm.

    - 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.

- 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.

### 6.1.2. Primary Study Cohort - Stage 1, Visit 2: 1-Week Follow-up Visit (6-8 Days After Visit 1) (*applicable to consenting PBMC subjects at PBMC collection sites only)*

- Review the subject's e-diary data.

- Record nonstudy vaccinations as described in Section 5.8.4.

- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays.
- 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.

### 6.1.3. Primary Study Cohort - Stage 1, Visit 2: 1-Month Follow-up Visit (28-35 Days After Visit 1) (*applicable to all subjects*)

- Ensure that the subject meets none of the subject withdrawal criteria as described in Section 6.5.
- 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.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).
- 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.

### 6.1.4. Primary Study Cohort - Stage 1, Visit 3: 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 6.5.
- 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.

### 6.1.5. Primary Study Cohort - Stage 1, Visit 4: 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 6.5.
- Collect a blood sample of approximately 50 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).
- 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 CRF.
- 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.

### 6.1.6. Primary Study Cohort - Stage 1, Visit 5: 12-Month Follow-up Visit (300-400 Days After Visit 1)

**For subjects not participating in Stage 2**:

- Collect a blood sample of approximately 25 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.

For the Primary Study Cohort - Stage 1 subjects invited and consenting to Stage 2 of this study, follow the procedures listed in Section 6.2.

## 6.2. Primary Study Cohort - Stage 2

### 6.2.1. Primary Study Cohort - Stage 2, Visit 5: 12-Month Follow-up Visit (300-400 Days After Visit 1)

Before any study-related procedures are performed, voluntary, written study-specific informed consent for the revaccination stage 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 Primary Study Cohort - Stage 2 ICD. A copy of this signed and dated ICD must be given to the subject. The source data must reflect that this informed consent was obtained before participation in the second stage of this study. Ideally, informed consent will be obtained prior to this visit.

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

- Perform physical examination including vital signs (weight, oral temperature, heart rate, and seated blood pressure), 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.

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

- 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.

- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).

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

- Prior to vaccination, collect a blood sample of approximately 25 mL for antibody assessment.

- Prior to vaccination, collect a blood sample of approximately 100 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only; see Section 3.1).

- 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 SIIV into the deltoid muscle of the right arm (see Table 6). Please refer to the IP manual for further instructions 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 (including time of onset) in the subject's source documents and on the AE page of the CRF, and on an SAE form if 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. Review the e-diary data in Trial Manager on a daily basis for the 14-day postvaccination period. Follow up on all severe reactions as described in Section 7.3.1.

- 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) at the injection site on the left arm.

    - 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.

- Schedule an appointment for the subject to return for the next study visit. Subjects consenting to PBMC collection will attend 1 week later for Visit 6A. All other subjects will attend Visit 6.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

### 6.2.2. Primary Study Cohort - Stage 2, Visit 6A: 1-Week Revaccination Follow-up Visit (6 to 8 Days After Visit 5) (*applies to subjects consenting to PBMC collection at PBMC collection sites only)*

- Review the subject's e-diary data.

- Record nonstudy vaccinations as described in Section 5.8.4.

- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).

- Collect a blood sample of approximately 50 mL for cellular assays.

- 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.

### 6.2.3. Primary Study Cohort - Stage 2, Visit 6: 1-Month Revaccination Follow-up Visit (28-35 Days After Visit 5) (*applies to all subjects*)

- Record nonstudy vaccinations as described in Section 5.8.4.

- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).

- Collect a blood sample of approximately 25 mL for antibody assessment.

- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).

- 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 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.

### 6.2.4. Primary Study Cohort - Stage 2, Visit 7: 3-Month Revaccination Follow-up Visit (84 to 105 Days After Visit 5) (*applies to all subjects*)

- Record nonstudy vaccinations as described in Section 5.8.4.
- Collect a blood sample of approximately 25 mL for antibody assessment.
- 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.

### 6.2.5. Primary Study Cohort - Stage 2, Visit 8: 6-Month Revaccination Follow-up Visit (168 to 210 Days After Visit 5) (*applies to all subjects*)

- Record nonstudy vaccinations as described in Section 5.8.4.
- Collect a blood sample of approximately 25 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRF.
- 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.

#### 6.2.6. Primary Study Cohort - Stage 2, Visit 9: 12-Month Revaccination Follow-up Visit (350 to 378 Days After Visit 5) (*applies to all subjects*)

- Record nonstudy vaccinations as described in Section 5.8.4.
- Collect a blood sample of approximately 25 mL for antibody assessment.
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

### 6.3. RSV Vaccine Month-0, Month-2 Cohort

#### 6.3.1. RSV Vaccine Month-0, Month-2 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 RSV Vaccine Month-0, Month-2 Cohort 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 the 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.
- Obtain any medical history of clinical significance.
- Assess and record tobacco usage.
- Record all current medications in source documents.
- Perform physical examination including vital signs (weight, height, oral temperature, heart rate, and seated blood pressure), 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.
- Record nonstudy vaccinations as described in Section 5.8.4.

- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the subject meets none of the temporary delay criteria as described in Section 4.3.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Obtain the subject's randomization number and investigational product container number using the IRT system. Either blinded site staff or unblinded site staff members may obtain this information.
- Prior to vaccination, collect a blood sample of approximately 25 mL for antibody assessment.
- Prior to vaccination, collect a blood sample of approximately 100 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only; see Section 3.1).
- Unblinded site staff member(s) will dispense/administer a 0.5-mL injection of investigational product into the deltoid muscle of the left arm (see Table 6). Please refer to the IP manual for further instruction on this process.
- Observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions (including time of onset) in the subject's source documents and on the AE page of the CRF, and on an SAE form if 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 1. Review the e-diary data in Trial Manager on a daily basis for the 14-day postvaccination period. Follow up on all severe reactions as described in Section 7.3.1.
- 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 1 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) at the injection site on the left arm.
  - 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.
- 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.

### 6.3.2. RSV Vaccine Month-0, Month-2 Cohort, Visit 2A: 1-Week Follow-up Visit (6 to 8 Days After Visit 1) (*applies to subjects consenting to PBMC collection at PBMC collection sites only)*

- Review the subject's e-diary data.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Collect a blood sample of approximately 50 mL for cellular assays.
- 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.

### 6.3.3. RSV Vaccine Month-0, Month-2 Cohort, Visit 2: 1-Month Follow-up Visit (28 to 35 Days After Visit 1) *(applies to all subjects)*

- 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.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Collect a blood sample of approximately 25 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).
- 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.

### 6.3.4. RSV Vaccine Month-0, Month-2 Cohort, Visit 3: Vaccination 2 Visit (54 to 66 Days After Visit 1) *(applies to all subjects)*

- 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.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Prior to vaccination, collect a blood sample of approximately 25 mL for antibody assessment.
- Prior to vaccination, collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only; see Section 3.1).

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

- Observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions (include time of onset) 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.

- 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 2. Review the e-diary data in Trial Manager on a daily basis for the 14-day postvaccination period. Follow up on all severe reactions as described in Section 7.3.1.

- 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 2 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) at the injection site on the left arm.

    - 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.

- 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.

### 6.3.5. RSV Vaccine Month-0, Month-2 Cohort, Visit 4A[a]: 1-Week Post-Vaccination 2 Follow-up Visit (6 to 8 Days After Visit 3) (*applies to subjects consenting to PBMC collection at PBMC collection sites only)*

- Review the subject's e-diary data.
- Record nonstudy vaccinations as described in Section 5.8.4.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Collect a blood sample of approximately 50 mL for cellular assays.
- 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.
- 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.

### 6.3.6. RSV Vaccine Month-0, Month-2 Cohort, Visit 4: 1-Month Post-Vaccination 2 Follow-up Visit (28 to 35 Days After Visit 3) *(applies to all subjects)*

- 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.
- Confirm understanding of and compliance with protocol requirements for contraception (male subjects only).
- Collect a blood sample of approximately 25 mL for antibody assessment.

- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).
- 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.

### 6.3.7. RSV Vaccine Month-0, Month-2 Cohort, Visit 5: 6-Month Follow-up Visit (168 to 210 Days After Visit 3) *(applies to all subjects)*

- Record nonstudy vaccinations as described in Section 5.8.4.
- Collect a blood sample of approximately 25 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays (*from consenting PBMC subjects at PBMC collection sites only)*.
- Record AEs as described in Section 8.
- 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 CRF.
- 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.

### 6.3.8. RSV Vaccine Month-0, Month-2 Cohort, Visit 6: 12-Month Follow-up Visit (350 to 378 Days After Visit 3) *(applies to all subjects)*

- Record nonstudy vaccinations as described in Section 5.8.4.
- Collect a blood sample of approximately 25 mL for antibody assessment.
- Collect a blood sample of approximately 50 mL for cellular assays (from consenting PBMC subjects at PBMC collection sites only).
- Record AEs as described in Section 8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

### 6.4. Unscheduled Reactogenicity Visits Following Vaccination

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 measuring on the left arm >20 measuring device units (>10.0 cm).
- swelling at the injection site measuring on the left arm >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) at the injection site on the left arm.
- 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 minimum and maximum diameters of redness on the left arm (if present).
- Measure 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) at the injection site on the left arm.
- Assess any injection site pain on the left arm that is present in accordance with the reactogenicity grading scale provided in Section 7.3.2.
- 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 7.3.4.
- 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 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.

## 6.5. 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. 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 safety profile and/or 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. CCI

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.

### 7.2. Immunogenicity

Blood samples will be collected as detailed in Section 6:

**Primary Study Cohort - Stage 1**: The total volume of blood collected from each subject will be approximately 225 mL over the course of the 1-year study. An additional approximately 300 mL will be collected from consenting PBMC subjects for the exploratory cellular analysis endpoints. The total volume of blood collected from subjects at these sites will be approximately 525 mL over the 1-year study period.

**Primary Study Cohort - Stage 2:** The additional blood volume collected from each subject participating in the revaccination stage is approximately 125 mL.

At PBMC collection sites, approximately 250 mL will be collected from consenting PBMC subjects for the exploratory cellular analysis endpoints. The total volume of blood collected from subjects at these sites will be approximately 375 mL during Stage 2.

**RSV Vaccine Month-0, Month-2 Cohort:** The total volume of blood collected from each subject will be approximately 150 mL over the course of the 1-year study.

At PBMC collection sites, approximately 450 mL will be collected from consenting PBMC subjects for the exploratory cellular analysis endpoints. The total volume of blood collected from subjects at these sites will be approximately 600 mL over the 1-year study period.

CCI

Whole blood will be taken for isolation of PBMCs for further research into the immune response (eg, B cells, plasmablasts, T cells).

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

### 7.2.1. RSV and Influenza Vaccine Antibody Testing

Sera collected will be assayed for RSV A– and RSV B–neutralizing antibody levels, anti-RSV prefusion F IgG levels, and immunoglobulin levels against nonvaccine RSV antigens. RSV A– and RSV B–neutralizing antibody levels will be determined for each blood sample and reported as the neutralizing titer. IgG levels will be determined against both RSV A and RSV B vaccine prefusion F antigens in a direct-binding Luminex immunoassay (dLIA) and reported as an anti-RSV prefusion F IgG antibody titer. Immunoglobulin levels against nonvaccine RSV antigens will also be tested by dLIA.

Hemagglutination inhibition antibody titers will be measured by the standard hemagglutination inhibition assay (HAI) for the influenza vaccine strains contained in the vaccine. H3N2-neutralizing antibody titers will also be investigated. Testing will be performed by a facility designated by Pfizer.

### 7.2.2. Exploratory Assays, Immunogenicity Assessments, and Assay Development

PBMCs isolated from whole blood will be used for evaluation of cellular immune responses to the RSV vaccine formulations. Exploratory analyses may include characterization of B-cell, plasmablast, and T-cell immune responses, and repertoire analyses.

A subset of subjects will be included in the whole blood collection procedural requirements for the exploratory cellular analysis endpoints for this study. The subset will be determined at the site level; specifically, those sites that have access to the appropriate specimen-processing laboratories will provide all subjects for the subset. It is anticipated that the subjects from the selected sites will constitute approximately 1/3 of the total number of randomized subjects.

Sera and plasma remaining after completion of the planned immunologic assays from blood draws taken throughout the study may be used for additional vaccine and infectious disease-related research, including exploratory immunologic assays for further characterization of the vaccine response.

CCI [redacted]

### 7.3. 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 each vaccination visit. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 7.3.1.

In the Primary Study Cohort - Stage 1, the first 4 subjects vaccinated in the study must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. Vaccination of subjects will be limited to a maximum of 6 subjects per day during the first week of enrollment (up to 30 vaccinated subjects in total) to maintain safety oversight.

For subjects enrolled, thereafter, irrespective of study cohort, blinded site staff must observe subjects for any acute reactions for at least 30 minutes after investigational product administration. Acute reactions after investigational product administration will be assessed and documented.

In addition, AEs, medically attended AEs (MAEs), AEs of specific interest, 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.

#### 7.3.1. Subject Electronic Diary

The subject will be asked to monitor and record local reactions (left arm), systemic events, fever, and antipyretics/pain medication used to treat symptoms, each evening for 14 days following each vaccination visit (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 in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be recorded by the investigator in the CRF. 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 designee) 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 7.4).

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.

### 7.3.2. Grading Scales

The grading scales used in this study to assess local reactions and systemic events (including fever) described in Tables 4 through 6 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.[11]

### 7.3.3. Local Reactions

Following each vaccination visit (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 (left arm) 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 on the left arm.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 20, and ≥21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 7 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 on the left arm will be prompted to contact the investigator to perform an unscheduled visit to assess the reaction. If the subject does not call the investigator, the site should call the subject.

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 7. 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.

### 7.3.4. Systemic Events

Following each vaccination visit (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 8 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 visit or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain) within 14 days after each vaccination visit. Study staff may also contact the subject to obtain additional information on 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. 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).

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 8. 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 |

**Table 8. Grading Scale for Systemic Events**

| | Mild Grade 1 | Moderate Grade 2 | Severe Grade 3 | Grade 4 [a] |
|---|---|---|---|---|
| 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.

### 7.3.5. 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 each vaccination visit (Day 1 through Day 14, where Day 1 is the day of vaccination) and at any time during the 14 days following vaccination 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 ≥102.1°F (≥39.0°C) will be prompted to contact the investigator to 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 9 below:

**Table 9. Ranges for Fever**

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

### 7.3.6. Use of Antipyretic/Pain Medication

For 14 days following each vaccination visit (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.

## 7.4. Stopping Rules

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 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 rules occur after administration of investigational RSV vaccine. E-diary data confirmed by the investigator as being entered by the subject in error will not contribute toward a stopping rule.

All formulations, with $Al(OH)_3$, with $CpG/Al(OH)_3$, or with sterile water, at a given dose will be evaluated for contribution to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the formulations at a given dose.

**Stopping Rule Criteria for All Formulations:**

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 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 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, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

### 7.4.1. 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. 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), as follows:

- SAEs: From informed consent until study completion.
- AEs:
  - Primary Study Cohort - Stage 1: Informed consent until Visit 2 (1 month after Vaccination 1). Thereafter MAEs will be collected.
  - Primary Study Cohort - Stage 2: Visit 5 until Visit 6 (1 month after Vaccination 2). Thereafter MAEs will be collected.
  - RSV Vaccine Month-0, Month-2 Cohort: Informed consent until Visit 4 (1 month after Vaccination 2). Thereafter MAEs will be collected.
- Occurrences of AEs of specific interest (refer to Table 10) will be recorded from administration of the investigational product until the subject completes the study, regardless of causality.

- Any AE occurring up to 48 hours after the blood draws at all study visits must be recorded and reported in the CRF.

- All AEs should be followed for resolution throughout the study. Stop dates are to be recorded in the CRF and source documents.

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. Adverse Events of Specific Interest

AEs of specific interest for safety monitoring include the occurrence of autoimmune disorders listed in Table 10. These events will be documented as AEs on the CRF and reported as SAEs if the event meets the seriousness criteria (Section 8.2.3). **Notification of AEs of specific interest to the Pfizer clinical team and completion of the AE CRF page should be done within 24 hours of investigator awareness.**

**Table 10. Autoimmune Diseases/Disorders**

| | |
|---|---|
| Gastrointestinal disorders | • Celiac disease<br>• Crohn disease<br>• Ulcerative colitis<br>• Ulcerative proctitis |
| Liver disorders | • Autoimmune cholangitis<br>• Autoimmune hepatitis<br>• Primary biliary cirrhosis<br>• Primary sclerosing cholangitis |
| Metabolic disorders | • Addison disease<br>• Autoimmune thyroiditis (including Hashimoto thyroiditis)<br>• Diabetes mellitus type 1<br>• Graves or Basedow disease |

## Table 10. Autoimmune Diseases/Disorders

| | |
|---|---|
| Musculoskeletal disorders | • Antisynthetase syndrome<br>• Dermatomyositis<br>• Juvenile chronic arthritis (including Still disease)<br>• Mixed connective tissue disorder<br>• Polymyalgia rheumatica<br>• Polymyositis<br>• Psoriatic arthropathy<br>• Relapsing polychondritis<br>• Rheumatoid arthritis<br>• Scleroderma, including diffuse systemic form and CREST syndrome<br>• Spondyloarthritis, including anklylosing spondylitis, reactive arthritis (Reiter syndrome), and undifferentiated spondyloarthritis<br>• Systemic lupus erythematosus<br>• Systemic sclerosis |
| Neuroinflammatory disorders | • Acute disseminated encephalomyelitis, including site-specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis<br>• Cranial nerve disorders, including paralyses/paresis (eg, Bell palsy)<br>• Guillain-Barré syndrome, including Miller Fisher syndrome and other variants<br>• Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy<br>• Multiple sclerosis<br>• Narcolepsy<br>• Optic neuritis<br>• Transverse myelitis<br>• Myasthenia gravis, including Eaton-Lambert syndrome |
| Skin disorders | • Alopecia areata<br>• Autoimmune bullous skin diseases, including pemphigoid, pemphigus, and dermatitis herpetiformis<br>• Cutaneous lupus erythematosus<br>• Erythema nodosum<br>• Morphea<br>• Lichen planus<br>• Psoriasis<br>• Sweet syndrome<br>• Vitiligo |
| Vasculitides | • Large-vessel vasculitis, including giant cell arteritis such as Takayasu arteritis and temporal arteritis<br>• Medium-sized and/or small-vessel vasculitis, including polyarteritis nodosa, Kawasaki disease, microscopic polyangiitis, Wegener granulomatosis (granulomatosis with polyangiitis), Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger disease (thromboangiitis obliterans), necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis (type unspecified), Henoch-Schönlein purpura, Behçet syndrome, and leukocytoclastic vasculitis |

**Table 10. Autoimmune Diseases/Disorders**

| | |
|---|---|
| Others | • Antiphospholipid syndrome<br>• Autoimmune hemolytic anemia<br>• Autoimmune glomerulonephritis, including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangial proliferative glomerulonephritis<br>• Autoimmune myocarditis/cardiomyopathy<br>• Autoimmune thrombocytopenia<br>• Goodpasture syndrome<br>• Idiopathic pulmonary fibrosis<br>• Pernicious anemia<br>• Raynaud phenomenon<br>• Sarcoidosis<br>• Sjögren syndrome<br>• Stevens-Johnson syndrome<br>• Uveitis |

Abbreviations: CREST = calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; IgA = immunoglobulin A.

### 8.4.3. 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 this study. 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 aspartate aminotransferase (AST) and/or alanine aminotransferase (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.

### 8.4.4. 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.

#### 8.4.4.1. 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.

#### 8.4.4.2. 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.

#### 8.4.4.3. 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.

### 8.4.5. 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 |

#### 8.4.5.1. 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 reported by an unblinded member of the site staff to the assigned study team member as described in the Investigational Product Complaint section of the IP manual. 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. For medical device products not yet approved/registered anywhere in the world, product complaints should be forwarded 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). 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 analyses for both immunogenicity and safety data will be descriptive in nature.

### 9.1. Sample Size Determination

Sample size calculation is not based on any formal statistical hypothesis testing. Two (2) study cohorts will be examined. Approximately 250 subjects were enrolled in the Primary Study Cohort - Stage 1, and approximately 62 subjects will be enrolled in the RSV Vaccine Month-0, Month-2 Cohort. Refer to Table 4 for a detailed description of the number of subjects per group. Sample size for the Primary Study Cohort - Stage 2 is dependent upon the number of invited subjects who consent to revaccination at Month 12.

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 31 subjects in in a vaccine group, there is 80% 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=31 | N=62 | N=93 | N=217 |
|---|---|---|---|---|
| 0.5% | 0.14 | 0.27 | 0.37 | 0.66 |
| 1% | 0.27 | 0.46 | 0.61 | 0.89 |
| 2% | 0.47 | 0.71 | 0.85 | 0.99 |
| 3% | 0.61 | 0.85 | 0.94 | >0.99 |
| 5% | 0.80 | 0.96 | 0.99 | >0.99 |

Note: In this study, 31 subjects are planned to be vaccinated with a specific RSV formulation at each dose level. 62 subjects are planned to be vaccinated with a specific dose level of adjuvanted RSV vaccine, 93 subjects are the maximum number of subjects to be vaccinated at a dose level from all 3 formulations, and 217 subjects are the combined subjects from all formulations and dose levels of RSV vaccine.

## 9.2. Immunogenicity Analysis

Immunogenicity results will be summarized by vaccine group and by study cohort.

### 9.2.1. Immunogenicity Analysis Populations

For the immunogenicity analyses, 2 analysis populations will be defined for each study cohort: Primary Study Cohort - Stage 1, Primary Study Cohort - Stage 2, and the RSV Vaccine Month-0, Month-2 Cohort.

#### 9.2.1.1. Primary Study Cohort - Stage 1

- **Evaluable immunogenicity population:** In general, the subject must have been eligible for the study, have received both SIIV and RSV vaccinations or SIIV and placebo to which he or she was randomized, have had blood drawn within the prespecified time frames at the 1-month postvaccination follow-up visit, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

- **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.

#### 9.2.1.2. Primary Study Cohort - Stage 2

- **Evaluable immunogenicity population:** In general, the subject must have been eligible for the study, have received vaccination and revaccination (concomitant with SIIV) to which the subject was randomized, have had blood drawn within the prespecified time frames at the 1-month post-Vaccination 2 follow-up visit, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

- **mITT population:** A subject must have been randomized in Stage 1, consented to participate in Stage 2 and have at least 1 valid and determinate assay result related to the proposed analysis.

#### 9.2.1.3. RSV Vaccine Month-0, Month-2 Cohort

- **Evaluable immunogenicity population:** In general, the subject must have been eligible for the study, have received all vaccinations to which the subject was randomized, have had blood drawn within the prespecified time frames at the 1-month post-Vaccination 2 follow-up visit, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations.

- **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 according to the vaccine 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 and cohort. 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 to each available time point after vaccination for each vaccine group and cohort. The GMFR will be calculated as the mean difference of individual subject logarithmically transformed antibody levels (postvaccination minus prevaccination) 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.

To assess whether concomitant administration of RSV and influenza vaccines interferes with the immune response to SIIV, geometric mean ratios (GMRs) and associated 2-sided 95% CIs will be calculated for HAI strains in SIIV by comparing sera drawn from subjects vaccinated with SIIV concomitantly with, for example, RSV vaccine 60 μg + CpG/$Al(OH)_3$ to sera drawn from subjects vaccinated with SIIV alone at 1 month after vaccination. This analysis will also be done for the other formulations and dose levels of RSV vaccine. 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 a 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 for the difference in percentages will be calculated between subjects immunized with SIIV concomitantly with each formulation and dose level of RSV vaccine and subjects immunized with SIIV and placebo at 1 month after vaccination. The CIs will be computed using the procedure of Chan and Zhang, using the standardized test statistic and gamma=0.000001.

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

Safety and tolerability results will be summarized by vaccine group and by study cohort.

All subjects receiving at least 1 dose 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, AEs of specific interest, 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, with 2-sided 95% exact CIs as appropriate.

The 3-tier approach will be used for the summary of AEs. Detailed definitions for each tier will be described in the SAP.

### 9.4. Analysis Timing

Three interim analyses will be conducted before the final analysis at the completion of the study:

- Primary Study Cohort - Stage 1

An analysis will be conducted when 1-month postvaccination immunogenicity data from all subjects in the Primary Study Cohort - Stage 1 are available. All available safety, tolerability, and immunogenicity data from subjects will be included in the analysis.

- Primary Study Cohort - Stage 2

An analysis will be conducted when 1-month post-Vaccination 2 immunogenicity data from all subjects in the Primary Study Cohort - Stage 2 are available. All available safety, tolerability, and immunogenicity data will be included in the analysis.

- RSV Vaccine Month-0, Month-2 Cohort

An analysis will be conducted when 1-month post-Vaccination 2 immunogenicity data from all subjects in this cohort are available. All available safety, tolerability, and immunogenicity data will be included in the analysis.

The results of these analyses will be used to select the most appropriate dose(s), formulation(s), and dosing schedule of the RSV vaccine for use in further studies in older adults.

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

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

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

### 9.5. Data Monitoring Committee(s)

This study will use an unblinded IRC and an 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 convene to review data on an ad hoc basis (eg, stopping rules are met, occurrence of suspected unexpected serious adverse reactions (SUSARs), unexpected safety or study conduct concerns). The committee will also review the results of any planned analysis when the required data are available.

The E-DMC will review study data according to the charter and any time a stopping rule is met, or other safety concern is identified.

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 institutional review board (IRB)/ethics committee (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.

### 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 investigational product 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

1. Hall CB, Simőes EAF, Anderson LJ. Clinical and epidemiologic features of respiratory syncytial virus. In: Anderson LJ, Graham BS, eds. *Challenges and Opportunities for Respiratory Syncytial Virus Vaccines*. Berlin/Heidelberg, Germany: Springer-Verlag Berlin Heidelberg; 2013:39-57. *Curr Top Microbiol Immunol*. 2013;372:39-57. doi:10.1007/978-3-642-38919-1_2.

2. Shi T, McAllister DA, O'Brien KL, et al; for RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet.* 2017;390(10098):946-958. doi:10.1016/S0140-6736(17)30938-8.

3. Walsh EE, Falsey AR. Respiratory syncytial virus infection in adult populations. *Infect Disord Drug Targets*. 2012;12(2):98-102.

4. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis*. 2012;206(1):56-62.

5. American Academy of Pediatrics. Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Policy statement: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2):415-420.

6. Prescott WA Jr, Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. *Pharmacoeconomics*. 2010;28(4):279-293.

7. Walsh EE, Peterson DR, Falsey AR. Risk factors for severe respiratory syncytial virus infection in elderly persons. *J Infect Dis.* 2004;189(2):233-238.

8. Boraschi D, Italiani P. Immunosenescence and vaccine failure in the elderly: strategies for improving response. *Immunol Lett.* 2014;162(1 pt B):346-353.

9. Scheiermann J, Klinman DM. Clinical evaluation of CpG oligonucleotides as adjuvants for vaccines targeting infectious diseases and cancer. *Vaccine*. 2014;32:6377-6389.

10. Heplisav-B. Food and Drug Administration Website. https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm584752.htm. Updated 13 Nov 2017; accessed 11 Dec 2017.

11. Food and Drug Administration, Center for Biologics Evaluation and Research. *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.* Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

## 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 |
| CBER | Center for Biologics Evaluation and Research |
| CI | confidence interval |
| CK | creatine kinase |
| COPD | chronic obstructive pulmonary disease |
| CRA | clinical research associate |
| CRF | case report form |
| CSA | clinical study agreement |
| CT | clinical trial |
| DILI | drug-induced liver injury |
| dLIA | direct-binding Luminex immunoassay |
| EC | ethics committee |
| e-diary | electronic diary |
| 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 |
| 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 |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HD | high-dose |
| HIV | human immunodeficiency virus |
| HRSV | *Human respiratory syncytial virus* |
| ICD | informed consent document |
| ICH | International Council for Harmonisation |
| ID | identification |
| IgG | immunoglobulin G |
| IND | investigational new drug application |
| INR | international normalized ratio |
| IP | investigational product |
| IRB | institutional review board |
| IRC | internal review committee |
| IRT | interactive response technology |
| IUD | intrauterine device |
| IUS | intrauterine system |
| IWR | interactive Web-based response |

| Abbreviation | Term |
|---|---|
| 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 |
| NHP | nonhuman primate |
| PBMC | peripheral blood mononuclear cell |
| PCD | primary completion date |
| PI | principal investigator |
| PT | prothrombin time |
| RCDC | reverse cumulative distribution curve |
| RNA | ribonucleic acid |
| RSV | respiratory syncytial virus |
| RSV vaccine | respiratory syncytial virus stabilized prefusion F subunit vaccine |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SIIV | seasonal inactivated influenza vaccine |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SRM | study reference manual |
| SUSAR | suspected unexpected serious adverse reaction |
| TBili | total bilirubin |
| TLR9 | Toll-like receptor 9 |
| ULN | upper limit of normal |
| US | United States |

# Document Approval Record

| | |
|---|---|
| **Document Name:** | C3671002 Clinical Protocol Amendment 3 Clean Copy, 22 Aug 2019 |
| **Document Title:** | C3671002 Clinical Protocol Amendment 3 Clean Copy, 22 Aug 2019 |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| PPD | 28-Aug-2019 13:24:07 | Final Approval |
| PPD | 28-Aug-2019 18:21:34 | Final Approval |