Protocol 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

Statistical Analysis Plan
(SAP)

Version: 3

Date: 15 Jun 2020

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LIST OF TABLES

1. VERSION HISTORY

This statistical analysis plan (SAP) for Study C3671001 is based on the protocol (Amendment 2) dated 11 Jun 2019.

Table 1.   Summary of Major Changes in SAP Amendments

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 31 Jul 2018	Amendment 1 (05 Jun 2018)	Not Applicable	Not Applicable
2/ 10 Oct 2019	Amendment 2 (11 Jun 2019)	Update according to protocol amendment 2	• CCI • CCI • CCI • CCI E 4 has also been updated after the approval of protocol amendment 2. Renamed the evaluable immunogenicity populations.

Table 1.   Summary of Major Changes in SAP Amendments

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
3/ 11 Jun 2020	Amendment 2 (11 Jun 2019)	CCI	- Used the appropriate SAP 2015 template, which does not include estimands. - Clarified the analysis cohorts, and defined the analysis population for each cohort. - CCI - CCI - Streamlined the structure on endpoints and analyses to follow the SAP template requirements. - Added local reactions and systemic events figures; added immunogenicity LLOQs for all assays. - Added the details of randomized subjects, vaccination visits, blood sample collections, and collections of e-diary data in each cohort. - Restructured and added the details of analyses for RSV A and RSV B neutralizing titer (NT), hemagglutination inhibition assay (HAI) CCI - Edited the wording for the General Methods section; restructured the Assessing Interference section into Section 5.2.2. - Added immunogenicity analyses for the sentinel and expanded cohorts, CCI

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671001. A brief description of the study design and the study objectives is given below. Subsequent sections describe analysis populations and give the definitions of the safety and immunogenicity endpoints followed by details of statistical reporting. A list of tables, listings, and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Objective

- To describe the safety and tolerability of a respiratory syncytial virus (RSV) vaccine given alone or concomitantly with seasonal inactivated influenza vaccine (SIIV).

2.1.2. Secondary Objectives

- Sentinel and expanded cohorts: To describe the immune responses elicited by an RSV vaccine alone (sentinel and expanded cohorts) or with SIIV (expanded cohort only).

- Expanded cohort: To describe the immune responses elicited by SIIV alone or with an RSV vaccine.

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2.2. Study Design

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

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

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

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

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

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

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

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

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

In the sentinel cohort, approximate 168 subjects will receive a single intramuscular dose of the RSV vaccine candidate with or without Al(OH)$_3$ or placebo at Vaccination 1. Central randomization will take place in a 3:3:1 ratio for each dose level, by age stratum.

In the expanded cohort, 1014 subjects will be randomized equally across all dose/formulation levels, with or without SIIV, by age group via center-based randomization. This will include a total of 13 groups with an equal randomization ratio. Subjects in this cohort will receive 2 intramuscular injections at Visit 1 (Vaccination 1) and 1 intramuscular injection at Visit 2 (Vaccination 2). ██████████████████████████████

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For both sentinel-cohort and expanded-cohort subjects, key safety data include electronic diary (e-diary) reports of local reactions and systemic events that occur within 14 days after Vaccination 1 (RSV vaccine or placebo). Adverse events (AEs) are collected from informed consent until 1 month after Vaccination 1 (Visit 3 for the sentinel cohort); and from consent until 1 month after Vaccination 2 (Visit 3 for the expanded cohort). AEs occurring up to 48 hours after blood draws are also collected. Medically attended AEs (MAEs) are collected after the AE collection period. Serious adverse events (SAEs) are being collected for all subjects from informed consent through 12 months after Vaccination 1.

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Blood samples are collected from all subjects for antibody testing. For sentinel-cohort subjects, blood samples are collected before Vaccination 1 and 2 weeks and 1, 2, 3, 6, and 12 months after Vaccination 1. For expanded-cohort subjects, blood samples for antibody testing are collected before Vaccination 1 and 1, 2, 3, 6, and 12 months after Vaccination 1.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Sentinel and Expanded Cohorts:

- Local reactions within 14 days after Vaccination 1.

- Systemic events within 14 days after Vaccination 1.

- AEs within 1 month after Vaccination 1.

- MAEs and SAEs through 12 months after Vaccination 1.

Expanded Cohort:

- AEs within 1 month after Vaccination 2.

3.1.1. Local Reactions

The local reactions reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 14 after vaccination, where Day 1 is the day of vaccination with RSV vaccine or placebo (Visit 1 for the sentinel/expanded cohort; CCI ██████████████████████ ████████████████ This section describes derivations with details for the assessment of local reactions: any presence, maximum severity, duration, and onset day of local reactions, in addition to presence of severe local reactions on each day.

3.1.1.1. <u>Presence of Local Reactions</u>

For the summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 14 after Vaccination 1 CCI ████████████████ where Day 1 is the day of vaccination, the following 2 variables are required in order to compute the proportions:

1. Presence (yes or no) of <u>each</u> local reaction on any day (Day 1 through Day 14).

   The derivation is described in Table 2.

Table 2.   Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Days 1 -14)	Subject reports the reaction as "yes" on any day (Days 1-14).	Subject reports the reaction as "no" on all 14 days or as a combination of "no" and "missing" on all 14 days.	Subject reports the reaction as "missing" on all 14 days.

a.   The variable will be defined for each of the 3 local reactions.

2. Presence (yes or no) of <u>any</u> local reaction on any day (Day 1 through Day 14);

   For any local reaction on any day, a similar definition can be applied as given in Table 3.

Table 3.   Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Days 1-14)	Subject reports any local reaction as "yes" on any day (Days 1-14).	Subject reports the reaction as "no" on all 14 days or as a combination of "no" and "missing" on all 14 days for all 3 local reactions.	Subject reports all local reactions as "missing" on all 14 days.

3.1.1.2. Maximum Severity of Local Reactions

The grading of local reactions is listed in Table 4.

Table 4.   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 and thus not reported from the e-diary.

The following 2 variables are required in order to compute the proportions of subjects reporting maximum severity.

1. Maximum severity of <u>each</u> local reaction on any day (Day 1 through Day 14).

    The maximum severity (highest grading) of each local reaction within 14 days after vaccination will be derived. The maximum severity will be derived as follows:

    = "Missing," if values are missing for all days (Days 1-14);

    = 0, if the subject reports all reactions as "no" or a combination of "missing" and "no" for all days (Days 1-14);

    = Highest grade (maximum severity) within 14 days after vaccination, if the answer is not "no" for at least 1 day.

2. Maximum severity of <u>any</u> local reaction on any day (Day 1 through Day 14).

    The maximum severity for any local reaction will be derived as follows:

    = "Missing," if values are missing for all days (Days 1-14) across all 3 local reactions;

    = 0, if the subject reports all reactions as "no" or a combination of "missing" and "no" for all days (Days 1-14) for any individual local reaction;

    = Highest grade (maximum severity) within 14 days after vaccination, if the answer is not "no" for at least 1 day for at least 1 local reaction.

3.1.1.3. Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as (resolution date of reaction – start date of reaction + 1). Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the subject diary-recording period (end date collected on the case report form [CRF]), unless chronicity is established. However, if an event is ongoing at the time of a subsequent vaccination with RSV vaccine or its placebo control, the end date/day for the ongoing event will be the date/day that the next vaccination with RSV vaccine or its placebo control is administered, which will be used for the computation of the duration. If there is no known end date, the duration will be considered unknown and set to "missing." Subjects with no reported reaction have no duration.

3.1.1.4. Onset Day of Each Local Reaction

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if a subject reports changes in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.5. Presence of Severe Local Reaction on Each Day

Presence (yes or no) of any severe local reaction on each of the 14 days (Day 1 through Day 14) follows the derivation as describe in Table 5.

Table 5.   Derived Variables for Any Severe Local Reaction on Each Day

Variable	Yes (1)	No (0)	Missing (.)
Any severe local reaction on a specific day	Subject reports the severe reaction as "yes" on a specific day for any of the 3 local reactions.	Subject reports local reactions as any of the following: "no," "mild," or "moderate" (for 1-3 of the reactions) or missing (for 1-2 of the reactions) on that specific day.	Subject reports all 3 local reactions as "missing" on that specific day.

3.1.2. Systemic Events

Systemic events, including fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain, are reported via e-diary from Day 1 through Day 14 after Vaccination 1 CCI where Day 1 is the day of vaccination with RSV vaccine or placebo (Visit 1 for the sentinel/expanded cohort; CCI The derivations below for systemic events will be handled similarly to the way local reactions are handled for presence, severity level, duration, onset day, and severe systemic events on each day.

1.   Presence (yes or no) of each systemic event on any day (Day 1 through Day 14);

2. Presence (yes or no) of <u>any</u> systemic event on any day (Day 1 through Day 14);

3. Maximum severity of <u>each</u> systemic event on any day (Day 1 through Day 14);

4. Maximum severity of <u>any</u> systemic event on any day (Day 1 through Day 14);

5. Duration of <u>each</u> systemic event;

6. Onset day of <u>each</u> systemic event;

7. Presence (yes or no) of <u>any</u> severe systemic event on each of the 14 days.

The systemic events gradings are provided in Table 6.

Table 6.   Grading Scale for Systemic Events

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

a.   Grade 4 assessment should be made by the investigator using the AE severity grading scale. The assessment will be collected on the AE case report form, thus not included in the systemic event analysis.

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. Any temperature recorded as <95.0°F (35.0°C) or >107.6°F (42.0°C) will be treated as a data entry error and excluded from the analyses. For reporting purposes, fever will be analyzed using the following temperature ranges:

- 38.0°C to 38.4°C (100.4°F – 101.1°F)

- 38.5°C to 38.9°C (101.2°F – 102.0°F)

- 39.0°C to 40.0°C (102.1°F – 104.0°F)

- >40.0°C (>104.0°C)

3.1.3. Use of Antipyretic/Pain Medication

Antipyretic/pain medications used to treat symptoms are recorded in the e-diary. This variable will be presented along with the systemic event summary, but not counted as a systemic event. The following variables will be derived:

1. Use of antipyretic/pain medication on "any day (Days 1-14)" after vaccination.

2. Duration of use of antipyretic/pain medication after vaccination.

3. Onset day of antipyretic/pain medication use after vaccination.

3.1.4. Adverse Events

AE reporting will be based on the specific reporting period. Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer Vaccine data standard rules.

As this is a Phase 1/2 study, with limited sample size included in each vaccine group, the value of applying the 3-tier approach is limited. Therefore, because of a small number of subjects in each dose/formulation group, safety assessment may be best carried out using descriptive statistics.

For AEs within 1 month after each vaccination, the interval calculation will be based on the study visit. Table 7 includes all AE intervals for each cohort. Any AEs with start date occurring within the lower bound and upper bound (inclusive) are included in the interval. It should be noted that Visit 2 and Visit 8 include intramuscular vaccination, thus AEs with start date at Visit 2 should be included in the next interval (AEs within 1 month after Vaccination 2). For consistency, this is applied to all intervals.

Table 7.   AE Analysis Interval

Cohort	Interval	AE Start Date Lower Bound (Inclusive)	AE Start Date Upper Bound (Inclusive)
Sentinel cohort	AEs within 1 month after Vaccination 1	Visit 1	The day before Visit 3
Expanded cohort	AEs within 1 month after Vaccination 1	Visit 1	The day before Visit 2[a]
Expanded cohort	AEs within 1 month after Vaccination 2	Visit 2	The day before Visit 3
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a.   This visit includes a vaccination.

The following derivations/summaries will be included for each of the above:

1. Proportions of subjects reporting AEs during this interval summarized for each system organ class and preferred term (and "any event"), separately.

2. Proportion of subjects reporting any AE during this interval.

3. Proportion of subjects reporting any MAE during this interval.

4. Proportion of subjects reporting any SAE during this interval.

5. Proportion of subjects reporting any related AE during this interval.

6. Proportion of subjects reporting any severe AE during this interval.

7. Proportion of subjects reporting any intermediate AE. Intermediate AE is defined as an AE reported within the first 30 minutes after vaccination.

8. Proportion of subjects reporting any AE leading to withdrawal during this interval.

3.1.5. Medically Attended Adverse Events

MAEs are collected after the AE collection period. Any MAEs with start date occurring within the lower bound and upper bound (inclusive) are included in the interval. Table 8 describes how the MAE analysis intervals are determined by study visits in each cohort. The following MAE-related variables will be derived:

1. Proportion of subjects reporting any MAE during this interval.

2. Proportions of subjects reporting MAEs during this interval summarized for each system organ class and preferred term, separately.

Table 8.   MAE Analysis Interval and Derivation

Cohort	Interval	Start Date Lower Bound	Start Date Upper Bound
Sentinel cohort	MAEs through 12 months after Vaccination 1	Visit 1	Visit 7
Expanded cohort	MAEs through 12 months after Vaccination 1	Visit 1	Visit 6
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3.1.6. Serious Adverse Events

SAEs are collected throughout the study. Any SAEs with start date occurring within the lower bound and upper bound (inclusive) are included in the interval. Table 9 describes how the SAE analysis intervals are determined by study visits in each cohort. The following SAE-related variables will be derived:

1. Proportion of subjects reporting any SAE during this interval.

2. Proportions of subjects reporting SAEs during this interval summarized for each system organ class and preferred term, separately.

Table 9.   SAE Analysis Interval and Derivation

Cohort	Interval	Start Date Lower Bound	Start Date Upper Bound
Sentinel cohort	SAEs through 12 months after Vaccination 1	Visit 1	Visit 7
Expanded cohort	SAEs through 12 months after Vaccination 1	Visit 1	Visit 6
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3.2. Secondary Endpoint(s)

Sentinel Cohort:

- RSV A– and RSV B–neutralizing antibody titers measured before Vaccination 1 and 2 weeks and 1, 2, 3, and 6 months after Vaccination 1.

Expanded Cohort:

- RSV A– and RSV B–neutralizing antibody titers measured before Vaccination 1 and 1, 2, 3, and 6 months after Vaccination 1.

- Hemagglutination inhibition assay (HAI) titers for all strains in the SIIV measured before and 1 month after SIIV administration.

3.2.1. RSV A– and RSV B–Neutralizing Antibody Titers

RSV A– and RSV B–neutralizing antibody titers will be determined on all sera collected at applicable visits for antibody testing.

Titers above the lower limit of quantitation (LLOQ) are considered accurate and their quantitated values will be reported. Refer to Section 5.3.2 for LLOQs. Titers below the corresponding LLOQ or denoted as below the limit of quantitation (BLQ) will be set to $0.5 \times$ LLOQ for analysis. Missing assay results will not be imputed.

In addition to titer, the neutralizing titer (NT) fold rise from before vaccination to each time point after the vaccination will be derived for both RSV A and RSV B as detailed below:

1. For the sentinel cohort: NT fold rise will be derived from before Vaccination 1 to each time point after Vaccination 1 with NT assay performed (2 weeks and 1, 2, 3, 6, and 12 months after Vaccination 1).

2. For the expanded cohort: NT fold rise will be derived from before Vaccination 1 to each time point after Vaccination 1 with NT assay performed (1, 2, 3, 6, and 12 months after Vaccination 1).

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For calculating a fold rise, < LLOQ will be converted to ½ LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only one of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

3.2.2. HAI Titers

Hemagglutination inhibition antibody titers will be measured by the standard HAI for the 4 influenza vaccine strains contained in the SIIV. The assay will have LLOQ = 1:10 for each strain.

For the expanded cohort: HAI fold rise will be derived from before SIIV to 1 month after SIIV for each strain tested. The visit numbers will be different for the different vaccine groups.

- For subjects in the coadministration groups (RSV vaccine and SIIV at Visit 1), the fold rise will be the ratio of Visit 2 to Visit 1.

- For subjects in the sequential-administration groups (SIIV after RSV vaccine, or SIIV at Visit 2), the fold rise will be the ratio of Visit 3 to Visit 2. If Visit 2 data are not available, Visit 1 data will be used.

In addition to the HAI titer and HAI fold rise, 2 binary variables will be derived for each of the influenza strains tested:

1. HAI seroprotection before and after SIIV vaccination: HAI titer is ≥1:40.

2. HAI seroconversion after SIIV vaccination:

   a. If the HAI titer is <1:10 (LLOQ for HAI) before SIIV administration, seroconversion is achieved if the postvaccination titer is ≥1:40.

   b. If the HAI titer is ≥1:10 before SIIV administration, seroconversion is achieved if the fold rise from the pre-SIIV titer to the postvaccination titer is ≥4.

The pre-SIIV and post-SIIV data have similar visit assignments as the fold-rise derivation.

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3.5. Baseline Variables

3.5.1. Baseline Definition

Day 1 is defined as the day of vaccination and start of the reporting period for local reactions and systemic events in the e-diary.

3.5.2. Demographics, Smoking History, and Medical History

Demographic variables collected include sex, race, ethnicity, and date of birth. Age at the time of vaccination (in years) will be derived based on birthday. For example, if the vaccination date is 1 day before the subject's 19th birthday, the subject is 18 years old.

Medical history of clinical significance will be collected and categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

Subject smoking history is also collected before Vaccination 1.

3.6. Safety Endpoints

Additional safety endpoints not covered in Section 3.1 and details of safety endpoints derivation are described in this section.

3.6.1. Laboratory Data

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

Assessments will include:

- Hematology: hemoglobin, complete blood count with differential, and platelets.

- Blood chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.

The grade change from Visit 0 to Visit 2 for each laboratory assessment will be derived. This should include all combinations of grading between the 2 visits. For example:

1. Within normal range to Grade 1

2. Remaining normal

3. Remaining Grade 1

4. Grade 1 to within normal range

3.7. Study Conduct

3.7.1. E-Diary Completion

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic/pain medication are present for any day. If all data are missing for all items on the e-diary for all 14 days (local reactions, systemic events, and use of antipyretic/pain medication) after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered transmitted for a given day if any data are present for that day.

3.7.2. Nonstudy Vaccines

Any nonstudy vaccinations given will be recorded in the CRF from the signing of the informed consent (ICD) to the 12-month follow-up visit (Visit 7 for sentinel-cohort subjects, Visit 6 for expanded-cohort subjects), CCI

Nonstudy vaccines will be categorized according to the latest version (at the time of reporting) of the World Health Organization (WHO) Drug Dictionary.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

Three analysis populations (evaluable RSV immunogenicity population, modified intent-to-treat [mITT] population, safety population) and the fourth analysis population (additional evaluable influenza immunogenicity population, as detailed below) will be defined for each of the C analysis cohorts: sentinel cohort, expanded cohort, combined sentinel and expanded cohorts. CCI

The evaluable immunogenicity population will be the primary analysis population for the immunogenicity endpoints evaluated for each cohort. Subjects will be included in the vaccine group as randomized in the analysis, which, by the population definition, is equivalent to the vaccine group corresponding to the vaccine received.

Analysis of immunogenicity results based on the mITT population will be considered supportive and will be performed only for critical endpoints, such as secondary endpoints, if there is enough difference (eg, >10%) between the evaluable immunogenicity population and the mITT population.

The safety population will be used for all analyses related to safety endpoints.

4.1. Sentinel Cohort

This cohort will include a total of 7 groups (6 vaccine groups and placebo), and 3 analysis populations will be defined. The placebo group will pool all subjects who were randomized or received placebo within each dose cohort.

4.1.1. Evaluable RSV Immunogenicity Population

This evaluable immunogenicity population will include subjects from the sentinel cohort who:

- Are eligible (have signed informed consent and met all inclusion/not met any exclusion criteria) and were randomized into the study;

- Have received RSV vaccine or placebo as randomized;

- Have a Visit 3 (1 month after vaccination) blood draw for assay testing within 27 to 42 days after Visit 1, inclusive, after vaccine administration (note: the 27- to 42-day interval is calculated as the Visit 3 date minus the Visit 1 date);

- Have at least 1 valid and determinate assay result for the 1-month postvaccination visit;

- Have no major protocol violation as determined by the study clinician.

Major protocol violations will be determined by clinical review. A major protocol violation is a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those subjects with protocol violations before any immunogenicity analysis is carried out.

4.1.2. mITT Population

All randomized subjects in the sentinel cohort who have at least 1 valid and determinate assay result related to the proposed analysis will be included in the mITT population.

4.1.3. Safety Population

All subjects in the sentinel cohort receiving at least 1 dose of the investigational products at Visit 1 will be included in the safety population. For the safety analyses, subjects will be analyzed according to the vaccine as administered.

4.2. Expanded Cohort

This cohort will include a total of 13 groups (12 vaccine groups and placebo), and 4 analysis populations will be defined.

4.2.1. Evaluable RSV Immunogenicity Population

This evaluable immunogenicity population will include subjects from the expanded cohort who:

- Are eligible (have signed informed consent and met all inclusion/not met any exclusion criteria) and were randomized into the study;

- Have received the vaccine (RSV vaccine or placebo) at Visit 1 as randomized;

- Have a Visit 2 (1 month after Vaccination 1) blood draw for assay testing within 27 to 42 days after Visit 1, inclusive, after vaccine administration (note: the 27- to 42-day interval is calculated as the Visit 2 date minus the Visit 1 date);

- Have at least 1 valid and determinate assay result for the 1-month postvaccination visit;

- Have no major protocol violation as determined by the study clinician.

4.2.2. Evaluable Influenza Immunogenicity Population

This evaluable immunogenicity population will include subjects from the expanded cohort who:

- Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and were randomized into the study;

- Have received the 2 vaccines (RSV vaccine or placebo with SIIV) at Visit 1 as randomized;

- Have received influenza vaccine at Visit 1 or Visit 2;

- Have a blood draw for assay testing within 27 to 42 days, inclusive, after influenza vaccination (note: the 27- to 42-day interval is calculated as the blood draw date minus the SIIV vaccination date. Refer to Section 3.2.2 for the corresponding visits based on the different vaccine groups);

- Have at least 1 valid and determinate assay result 1 month after influenza vaccination;

- Have no major protocol violation as determined by the study clinician.

This population will be the primary analysis population related to influenza assay results.

4.2.3. mITT Population

All randomized subjects in the expanded cohort who have at least 1 valid and determinate assay result related to the proposed analysis will be included in the mITT population.

4.2.4. Safety Population

All subjects in the expanded cohort receiving at least 1 dose of the investigational products at Visit 1 will be included in the safety population. For the safety analyses, subjects will be analyzed according to the vaccine as administered.

4.3. Combined Sentinel and Expanded Cohorts

This cohort will pool subjects from the sentinel cohort and expanded cohort. Only subjects who are randomized to receive SIIV at Visit 2 from the expanded cohort will be pooled with the sentinel cohort, across the dose/formulation groups. This cohort will include a total of 7 groups (6 vaccine groups and placebo), and 3 analysis populations will be defined.

4.3.1. Evaluable RSV Immunogenicity Population

This evaluable immunogenicity population will include subjects from the combined sentinel and expanded cohorts who:

- Are eligible (have signed informed consent and met all inclusion/not met any exclusion criteria) and were randomized into the study;

- Have received the vaccine (RSV vaccine or placebo) at Visit 1 as randomized;

- Have 1-month post–Vaccination 1 blood drawn for assay testing within 27 to 42 days after Visit 1, inclusive, after vaccine administration (note: the 27- to 42-day interval is calculated as the blood draw date minus the vaccination date);

- Have at least 1 valid and determinate assay result for the 1-month postvaccination visit;

- Have no major protocol violation as determined by the study clinician.

4.3.2. mITT Population

All randomized subjects in the combined sentinel and expanded cohorts who have at least 1 valid and determinate assay result related to the proposed analysis will be included in the mITT population.

4.3.3. Safety Population

All subjects in the in the combined sentinel and expanded cohorts receiving at least 1 dose of the investigational products at Visit 1 will be included in the safety population. For the safety analyses, subjects will be analyzed according to the vaccine as administered.

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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Statistical Hypotheses

This Phase 1/2 FIH study is designed to describe the safety, tolerability, and immunogenicity of RSV vaccine formulations in 2 age groups. No formal statistical hypothesis testing will be performed. An estimation approach will be used to assess the safety and immunogenicity objectives.

5.1.2. Statistical Decision Rules

Statistical decision rules will not be utilized in this study. All analyses are considered descriptive in nature.

5.2. General Methods

Safety data and immunogenicity data will be summarized by vaccine group for each cohort. All analyses will be descriptive in nature.

Unless otherwise stated, "95% CI" refers to 2-sided 95% CI in this document.

5.2.1. Analyses for Binary Data

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

1. The 95% CI for the proportion will be constructed by the Clopper-Pearson method described by Newcombe.[3] The 95% CI will be presented in terms of percentage.

2. The 95% CI for the difference in the proportions will be computed using the Miettinen and Nurminen method.[4] The 95% CI will be presented in terms of percentage.

5.2.2. Analyses for Continuous Data

Unless otherwise specified, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

The CI for the mean of the continuous variable will be constructed by the standard method based on Student's t distribution.

5.2.2.1. Geometric Mean Titer

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. Geometric mean titer (GMT) and associated 95% CI will be calculated at each available time point for each vaccine group and cohort. Geometric means and their 95% CIs will be derived by calculating means and CIs on the natural log scale based on the t distribution, then exponentiating the results.

5.2.2.2. Geometric Mean Fold Rise

Geometric mean fold rises (GMFRs) will be limited to subjects with nonmissing values at both visits. Individual subject antibody levels fold rise from one time point to another time point will be transformed in natural logarithm scale for analysis. Means and their 95% CIs on the natural log scale will be based on the 1-sample Student's t distribution. GMFRs and corresponding 95% CIs will calculated by exponentiating the results from the natural log scale.

5.2.2.3. Geometric Mean Ratio

The geometric mean ratio (GMR) will be calculated by transforming the group mean difference of the antibody levels in natural logarithm scale to original scale. 95% CI is also computed by exponentiating the CIs from the natural log scales using 2-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical reverse cumulative distribution curves (RCDCs) will plot the proportion of subjects with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the data point on the left side of the step.

5.2.2.5. Assessing Interference

To understand whether concomitant administration of influenza and RSV vaccines in the expanded cohort interferes with the immune response to RSV vaccine, the GMR with associated 95% CI for RSV A– and RSV B–neutralizing antibody titers between sera drawn from subjects vaccinated with RSV vaccine with or without concomitant SIIV at 1 month after Vaccination 1 will be calculated.

Using RSV vaccine 60 μg as an example, the GMR will be calculated as follows:

- Numerator: RSV vaccine 60 μg/SIIV+placebo; and denominator: RSV vaccine 60 μg/placebo+SIIV.

- Numerator: RSV vaccine 60 μg+$Al(OH)_3$/SIIV+placebo; and denominator: RSV vaccine 60 μg+$Al(OH)_3$/placebo+SIIV.

To understand whether concomitant administration of influenza and RSV vaccines in the expanded cohort interferes with the immune response to SIIV vaccine, the GMR with associated 95% CI for HAI for strains in SIIV by comparing sera drawn from subjects vaccinated with SIIV concomitantly with RSV vaccine at 1 month after Vaccination 1 or with SIIV alone at 1 month after Vaccination 2 will be calculated.

- Numerator: RSV vaccine 60 μg/SIIV+placebo; and denominator: placebo/placebo+SIIV.

- Numerator: RSV vaccine 60 μg+Al(OH)$_3$/SIIV+placebo, and denominator: placebo/placebo+SIIV.

- Numerator: RSV vaccine 60 μg/SIIV+placebo; and denominator: RSV vaccine 60 μg/placebo + SIIV.

- Numerator: RSV vaccine 60 μg+Al(OH)$_3$/SIIV+placebo; and denominator: RSV vaccine 60 μg+Al(OH)$_3$/placebo + SIIV.

Similar combinations and comparisons will be done for the RSV vaccine 120-μg and 240-μg dose levels.

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5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the safety rulebook summary.

Missing data handling rules on the safety data are described in detail in the corresponding endpoint sections.

5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 14-day e-diary is available, the "any day (Days 1-14)" data will be considered as nonmissing.

The reactogenicity data are collected through the e-diary, which does not allow subjects to skip the question. Therefore, for a specific day, if the e-diary data are transferred for that day, all of the reactogenicity data for the subject on that day are nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.1.

5.3.2. Immunogenicity Data

Any assays above LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis.

For calculating a fold rise, < LLOQ will be converted to 0.5 × LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only one of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

The LLOQs for each assay are listed in Table 10.

Table 10.   LLOQ Titers for All Assay

Serotype	LLOQ
NT RSV A–50%	50
NT RSV B–50%	70
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	0.55
HAI: A/CCI	10
HAI: A/CCI	10
HAI: B	10
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Abbreviations: HAI = hemagglutination inhibition assay; C G; CCI
LLOQ = lower limit of quantification; NT = neutralizing titer; CCI

Values for sera that are insufficient (QNS), indeterminate results, or values recorded as "not done" will be set to "missing." Additionally, any time point with no blood draws will not be included in the analysis. No imputation will be done for these missing values.

6. ANALYSES AND SUMMARIES

This section describes the analyses and summaries across all endpoints. In order to reconcile the protocol-specified endpoints (or estimands) and SAP template structure, the primary endpoints and secondary endpoints specified in the protocol are carried out in the "primary analysis" described in this section.

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For each of the C analysis sets (sentinel cohort, expanded cohort, combined sentinel and expanded cohorts, CCI, all safety and immunogenicity endpoints listed below will be summarized by age stratum, without combining the total age range. For the combined sentinel and expanded cohorts, the older age group will use a sentinel-cohort age range of 50 to 85 years.

6.1. Primary Endpoints

6.1.1. Local Reactions

6.1.1.1. Primary Analysis

Endpoint: Proportions of subjects reporting prompted local reaction within 14 days after vaccination.

- Analysis time points: Within 14 days after Vaccination 1.

- Analysis population: Safety population (sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Primary objective.

Reporting Results:

Proportions of subjects reporting each and any local reactions after Vaccination 1 will be summarized by maximum severity level. Confirmed e-diary errors will be excluded from the analysis.

For each cohort, the percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each vaccine group, by age stratum.

Figures: Bar charts with the proportions of subjects for each local reaction will be plotted for each vaccine group, by age stratum. The bar charts will be divided into severity subgroups to highlight the proportions of subjects by severity.

6.1.1.2. Additional Summary for Assessing Local Reactions After Vaccination 1

To support the assessment of local reactions, additional endpoints (as defined in Section 3.1.1) will be summarized. Confirmed e-diary errors will be excluded from these analyses.

Binary Endpoints

For each cohort, the percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each vaccine group by age stratum for the following endpoints:

- Subjects reporting any severe local reaction on each day and any day (Day 1 through Day 14).

Continuous Endpoints

For each cohort, the following endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group, by age stratum:

- o Duration of each systemic event after vaccination.

- o Onset day of each systemic event after vaccination.

- o Onset day of any systemic event after vaccination.

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6.1.2. Systemic Events

6.1.2.1. Primary Analysis

Endpoint: Proportions of subjects reporting prompted systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) within 14 days after vaccination.

- Analysis time points: Within 14 days after Vaccination 1.

- Analysis population: Safety population (sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Primary objective.

Reporting Results:

Proportions of subjects reporting each and any systemic events after Vaccination 1 will be summarized by maximum severity level. Confirmed e-diary errors will be excluded from the analysis.

For each cohort, the percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each vaccine group, by age stratum.

Figures: Bar charts with the proportions of subjects for each systemic event will be plotted for each vaccine group, by age stratum. The bar charts will be divided into severity subgroups to highlight the proportions of subjects by severity.

6.1.2.2. Additional Summary for Assessing Systemic Events

To support the assessment of systemic events, additional endpoints (as defined in Section 3.1.2) will be summarized for each vaccine group, by age stratum. Confirmed e-diary errors will be excluded from these analyses.

Binary Endpoints

For each cohort, the percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each vaccine group after Vaccination 1 for the following endpoints:

- Subjects reporting any severe systemic events on each day and any day (Day 1 through Day 14).

Continuous Endpoints

For each cohort, the following endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group, by age stratum:

- Duration of each systemic event after vaccination.

- Onset day of each systemic event after vaccination.

- Onset day of any systemic event after vaccination.

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6.1.3. AEs

6.1.3.1. Primary Analysis

Endpoint: Proportions of subjects reporting AEs.

- Analysis time points: Within 1 month after Vaccination 1 and within 1 month after Vaccination 2 (expanded cohort only).

- Analysis population: Safety population (sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Primary objective.

Reporting Results:

For each cohort, the percentage (%), the number of subjects, the denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI for subjects reporting any AE, for each system organ class, and each preferred term within system organ class, will be presented for each vaccine group, by age stratum.

6.1.3.2 Additional Summary for Assessing Adverse Events

To support the assessment of AEs, additional endpoints by category (related AE, severe AE, SAE, MAE, immediate AE, AE leading to withdrawal), as defined in Section 3.1.4, will be summarized for all listed analysis time points among applicable cohort analysis populations, using similar analysis methodology and appropriate reporting results.

If any nonserious AEs are reported to occur before vaccination or more than 1 month after vaccination (outside of the protocol-specified reporting window), they will not be summarized, but will be included in the AE listings.

For AEs reported within 1 month after Vaccination 1 among the sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts, each category will be compared between each RSV vaccine group and placebo, by age stratum. Between-group differences (RSV group – placebo group) in proportions and the associated 95% CIs will be provided using the Miettinen and Nurminen method.

Additionally, for the expanded cohort only, each category of AE reported within 1 month after Vaccination 1 will be compared between the coadministration (RSV and SIIV) and RSV groups within each dose/formulation, by age stratum. Between-group differences (RSV+SIIV group – SIIV group) in proportions and the associated 95% CIs will be provided using the Miettinen and Nurminen method.

Figures: Bar charts with the proportions of subjects for each category will be plotted for each vaccine group, by age stratum.

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6.1.4. SAEs

6.1.4.1. Primary Analysis

Endpoint: Proportions of subjects reporting SAEs.

- Analysis time points: Through 12 months after Vaccination 1.

- Analysis population: Safety population (sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Primary safety objective.

Reporting Results:

The percentage (%), the number of subjects (n), the denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI for subjects reporting any SAEs, for each system organ class, and for each preferred term within system organ class, will be presented for each vaccine group, by age stratum.

Figures: None.

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6.1.5. MAEs

MAEs will be analyzed in a similar way as SAEs (Section 6.1.4).

6.2. Secondary Endpoint(s)

The evaluable immunogenicity population definition included a required window of 1 month after the vaccination (either RSV or SIIV). However, almost all RSV immunogenicity endpoints are evaluated at multiple time points. To ensure a true description of immune response kinetics, the following rules are used for the time points included in the analyses:

1. 1 Month after Vaccination 1 – 27 to 42 days after Vaccination 1 (per the evaluable immunogenicity definition, with an additional relaxation of -1 to +7 days compared with the protocol-required window)

2. 2 Weeks after Vaccination 1 – 11 to 21 days after Vaccination 1 (relaxation of ±3 days)

3. 2 Months after Vaccination 1 – 49 to 77 days after Vaccination 1 (relaxation of ±1 week)

4. 3 Months after Vaccination 1 – 77 to 112 days after Vaccination 1 (relaxation of -1 to +1 week)

5. 6 Months after Vaccination 1 – 154 to 224 days after Vaccination 1 (relaxation of -2 to +2 weeks)

6. 12 Months after Vaccination 1 – 336 to 392 days after Vaccination 1 (relaxation of -2 to +2 weeks)

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6.2.1. RSV A– and RSV B–Neutralizing Antibody Titers

6.2.1.1. Primary Analysis

Endpoint: RSV A– and RSV B–neutralizing antibody titers.

- Analysis time points: From before to up to 6 months after Vaccination 1.

- Analysis populations: Evaluable RSV immunogenicity population (sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

Reporting Results:

GMTs at the above-mentioned time point and associated 95% CIs will be summarized by vaccine group for both RSV A– and RSV B–neutralizing antibody titers. Also, GMFRs from before Vaccination 1 to each above-mentioned time point and associated 95% CIs will be summarized by vaccine group for both RSV A– and RSV B–neutralizing antibody titers.

Figures:

RCDCs for RSV A– and RSV B–neutralizing antibody titers for the 2 time points (before Vaccination 1 and 1 month after Vaccination 1), by vaccine group, will be generated for each age stratum among the combined sentinel and expanded cohorts.

6.2.1.2. Additional Summary

For the sentinel cohort, expanded cohort, and combined sentinel and expanded cohorts, GMTs at all other applicable visits after Vaccination 1 will be summarized along with associated 95% CIs for each vaccine group, by age stratum, for both RSV A– and RSV B–

neutralizing antibody titers. Additionally, all fold rises specified in Section 3.2.1 will be summarized with GMFRs and associated 95% CIs.

The following comparisons will be made in order to assess the interference of SIIV coadministration with the immune response induced by RSVpreF among the expanded cohort:

- GMTs for RSV A NT and RSV B NT will be compared between the RSVpreF with SIIV group and the RSVpreF-only (or SIIV after RSVpreF) group for each dose/formulation, by age stratum. GMRs and associated 95% CIs will be calculated from 1 month through 12 months after Vaccination 1.

Figures:

For the combined sentinel and expanded cohorts, NT GMT kinetics for each vaccine group will be plotted across all visits, by age stratum.

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6.2.2. HAI Titers

6.2.2.1. Primary Analysis

Endpoint: HAI titers for all strains tested.

- Analysis time points: Before and 1 month after SIIV vaccination.

- Analysis populations: Evaluable influenza immunogenicity population (expanded cohort).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

Reporting Results:

GMTs before and 1-month after SIIV vaccination (Visit 1 or 2) and associated 95% CIs will be summarized by vaccine group for each influenza strain tested, by age stratum. Also, GMFRs from before to 1 month after SIIV and associated 95% CIs will be summarized by vaccine group for each strain tested.

Figures:

RCDCs for each influenza strain testing at the 2 time points (before SIIV and 1 month after SIIV) by vaccine group will be generated by age stratum among the expanded cohort
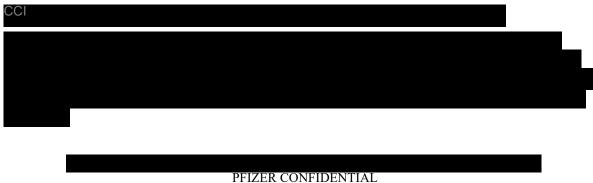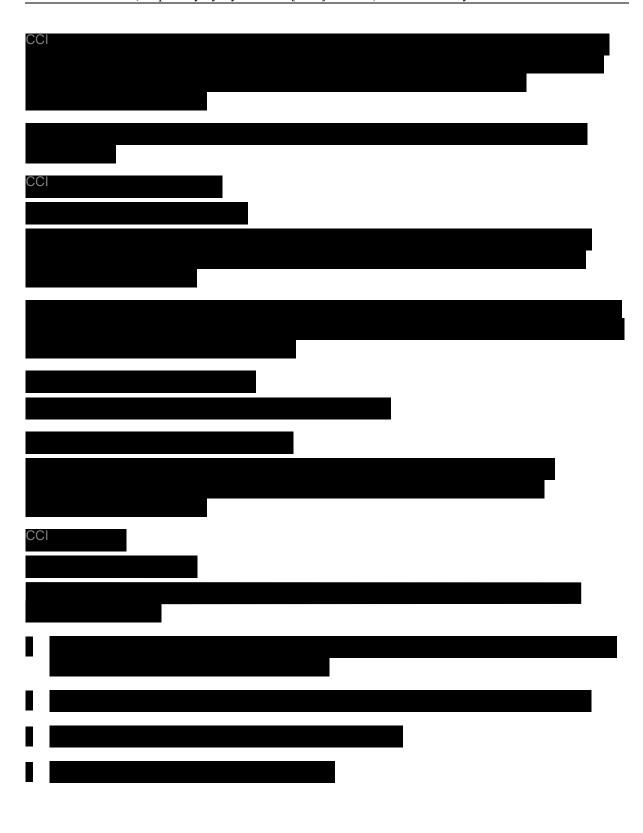
6.2.2.2. Additional Summary

The seroprotection rate before SIIV (Visit 1 or 2) and 1 month after SIIV, and seroconversion rates from before SIIV to 1 month after SIIV, will be summarized with n, percentage (%), and 95% CI, among the expanded cohort.

The following comparisons will be made in order to assess the interference of RSV vaccine coadministration with the SIIV immune response (expanded cohort only):

- For each RSVpreF dose/formulation, 1-month post-SIIV GMTs from the SIIV coadministration group will be compared with SIIV administered after the same RSVpreF dose/formulation, for each influenza strain tested. GMRs and associated 95% CIs will be calculated.

- For each RSVpreF dose/formulation with SIIV coadministration, 1 month post-SIIV GMTs will be compared with the control group that had SIIV administered after placebo, for each influenza strain tested. GMRs and associated 95% CIs will be calculated.

- For each RSVpreF dose/formulation with SIIV coadministration, 1-month post-SIIV GMTs will be compared with the pooled group without coadministration of RSVpreF (including the control group that had SIIV administered after placebo, and SIIV administered after RSVpreF) for each influenza strain tested. GMRs and associated 95% CIs will be calculated.

The evaluable influenza immunogenicity population will be used. However, the mITT population may be used for some comparison.

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6.5. Subset Analyses

For each analysis set (sentinel cohort, expanded cohort, combined sentinel and expanded cohorts,CCI subgroup analysis for immunogenicity results may be carried out for the younger age group (18-49 years of age), by sex, provided that the numbers of subjects in the subgroups are sufficient for a meaningful data summary.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

6.6.1.1. Demographics and Smoking History

For each cohort, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity) will be generated for each vaccine group, as well as the total subjects, based on safety population.

The proportions of subjects reporting as "current smoker," "ex-smoker," and "never smoked" will be summarized in a similar way.

Summary data may also be presented for the evaluable immunogenicity populations.

Subject data listings for demography and baseline characteristics data will also be listed.

6.6.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of subjects with at least 1 diagnosis, overall and at each system organ class and preferred term level, may be summarized by vaccine group and for overall subjects included in the safety population for each cohort.

However, as medical history was mainly collected to ensure that subjects met study eligibility, this information may only be listed.

6.6.2. Study Conduct and Subject Disposition

The number and proportion of randomized subjects will be included in the subject disposition summary. In addition, subjects who completed each follow-up visit, and those who withdrew before the follow-up visit along with the reasons for withdrawal, will be tabulated by vaccine group and total subjects. The reasons for withdrawal will be those as specified in the database.

Subjects excluded from the evaluable immunogenicity and mITT populations will also be summarized with reasons for exclusion.

The summaries will be provided for each cohort by age stratum, as well as for combined age group.

Standard listings, included subjects who withdrew during the study, subjects excluded from analysis populations, subjects with major protocol violations, subjects who did not receive the vaccine as randomized, etc, will all be included.

6.6.2.1. E-Diary Completion

For each cohort, the number and percentage of vaccinated subjects with e-diary data transmitted for each day (Days 1 through 14) and for all days after Vaccination 1 and Vaccination 2 in the required reporting period may be summarized by vaccine group and for all subjects included in the safety population.

However, the e-diary transmission rate is relevant to monitoring study conduct. The summary may be omitted, as the information is included in reactogenicity listings.

6.6.2.2. Nonstudy Vaccines

Nonstudy vaccines taken after signing the informed consent through the end of the study will be categorized according to the WHO Drug Dictionary and may be summarized by vaccine group and for all subjects included in the safety population.

A listing may be used to replace the table.

6.7. Safety Summaries and Analyses

6.7.1. Additional Analyses of Adverse Events

All safety summaries are included in Section 6.1.

6.7.2. Laboratory Data

Descriptive summaries (counts and percentage) for laboratory parameter grading changes as defined in Section 3.6.1 will be provided by vaccine group for the sentinel cohort. Also, a listing of laboratory data will be generated.

7. INTERIM ANALYSES

The primary study results will be summarized after major data up to 12 months after Vaccination 1 are available. CCI However, interim analyses are planned before the CCI the completion of the study.

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

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

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

   An analysis will be conducted when 1-month post–Vaccination 1 RSV immunogenicity results from all subjects in the 18- to 49-year age group of the expanded cohort are available. All available safety, tolerability, and immunogenicity data for this age group will be included in the analysis. The analysis will be used to support decisions on dosage levels for the Phase 2 trial for the maternal indication.

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

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

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

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

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Assays may come in batches; therefore, some interim analyses may be performed in batches. One interim analysis may span multiple reporting events. Also, after the study team is unblinded to subject level data, some additional analyses may be conducted before the primary or final analysis to support other internal program-level decisions as needed. These additional analyses include tables and listings created specifically for the internal review committee (IRC) and external data monitoring committee (E-DMC).

Safety data will be summarized on an ongoing basis.

No multiplicity adjustments will be applied for any of the interim analyses as mentioned above.

8. REFERENCES

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