Protocol C3671006

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus Prefusion F Subunit Vaccine When Coadministered With Seasonal Inactivated Influenza Vaccine in Adults ≥65 Years of Age

Statistical Analysis Plan (SAP)

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 08 Sep 2021	Original 30 Aug 2021	N/A	N/A
2/ 23 Sep 2022	1/ 29 Aug 2022	1. Removed the definition of LLOQ per assay; the final LLOQ for the assay will be included in the assay data, as noted in the assay data transfer memo 2. Amended the study sample size from 2230 to 1400; changed the statement for declaring immunogenicity equivalence from 0.67 to 0.667 3. Clarified that the end date when a reaction is ongoing at the time of Vaccination 2 is the date of the day before Vaccination 2 in "Duration of Each Local Reaction" 4. Updated the blood sample collection window from "27 days to 42 days" to "25 days to 49 days" to allow a reasonable and more inclusive visit window 5. Clarified the randomized population is based on enrolled participants 6. Clarified the meaning of the study intervention for the reporting purpose; replaced "study intervention" with "vaccine group" throughout the document 7. Clarified that "racial designation" is included in the summary of baseline information and that the trial disposition summary is mainly based on the randomized participants 8. Adapted the wording used for describing the e-diary safety analysis; clarified the analysis of local reactions and systemic	1. Changed Section 5.3.2 2. Changed Section 2.2, Section 5.1.1, and Section 5.1.2 3. Updated Section 3.1.3.1.3 4. Updated Section 2.1.1.1, Section 2.1.1.2, and Section 4 5. Updated Section 4 6. Updated Table 2 and Section 4; changed throughout the document 7. Updated Section 3.3.2 and Section 6.5.1 8. Updated Section 6.1.3

Table 1. Summary of Changes			
Version/ Date	**Associated Protocol Amendment**	**Rationale**	**Specific Changes**
		events will be "by vaccine group as administered" 9. Updated the section title to "Nonstudy Vaccines;" clarified the summary of concomitant medications is mainly for nonstudy vaccines	9. Updated Section 6.5.3

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671006. 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, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 2.

Table 2. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To evaluate the safety profiles of RSVpreF when coadministered with SIIV (RSVpreF + SIIV) or administered 1 month after SIIV.	• Local reactions (redness, swelling, and pain at the injection site) self-reported on e-diaries for 7 days after vaccination. • Systemic events (fever, fatigue, headache, nausea, vomiting, diarrhea, muscle pain, and joint pain) self-reported on e-diaries for 7 days after vaccination. • AEs. • SAEs.	In participants receiving at least 1 dose of study intervention (RSVpreF, placebo, or SIIV) and having safety follow-up after vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after vaccination with RSVpreF or placebo. • The percentage of participants reporting prompted systemic events within 7 days after vaccination with RSVpreF or placebo.

Table 2. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
		• The percentage of participants reporting AEs within 1 month after each vaccination. • The percentage of participants reporting SAEs within 1 month after each vaccination.
Primary RSV Immunogenicity		
To demonstrate that the immune responses elicited by RSVpreF when coadministered with SIIV (RSVpreF + SIIV) are noninferior to those elicited by RSVpreF alone when administered 1 month after SIIV.	• RSV A and RSV B NTs.	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of NTs at 1 month after vaccination with RSVpreF for each RSV subfamily (A or B) in the coadministration group (RSVpreF + SIIV) to the sequential-administration group (RSVpreF alone).
Primary SIIV Immunogenicity		
To demonstrate that the immune responses elicited by SIIV when coadministered with RSVpreF (RSVpreF + SIIV) are noninferior to those elicited by SIIV alone.	• Strain-specific HAI titers. • H3N2-neutralizing antibody titers (if interpretable H3N2-HAI titers cannot be obtained).	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of the strain-specific HAI (or H3N2-neutralizing antibody) titers 1 month after vaccination with SIIV in the coadministration group (RSVpreF + SIIV) to the sequential-administration group (SIIV alone).

Table 2. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Secondary RSV Immunogenicity		
To describe immune responses elicited by RSVpreF when coadministered with SIIV or when administered alone	• RSV A and RSV B NTs.	In participants in compliance with the key protocol criteria (evaluable participants) from each vaccine group: • Geometric mean of the NTs for RSV A and RSV B before vaccination and at each applicable visit after vaccination with RSVpreF. • GMFR of the NTs for RSV A and RSV B from before vaccination to each applicable visit after vaccination with RSVpreF.
Secondary SIIV Immunogenicity		
To describe immune response elicited by SIIV when coadministered with RSVpreF or when administered alone.	• Strain-specific HAI titers. • H3N2-neutralizing antibody titers (if interpretable H3N2-HAI titers cannot be obtained).	In participants in compliance with the key protocol criteria (evaluable participants) from each vaccine group: • GMTs before vaccination and 1 month after vaccination with SIIV. • GMFR of strain-specific HAI titers (or H3N2-neutralizing antibody titers if interpretable H3N2-HAI titers cannot be obtained) from before vaccination to 1 month after vaccination with SIIV.
CCI [redacted]		
[redacted]	[redacted]	[redacted]
Exploratory SIIV Immunogenicity:		
To further describe immune responses elicited by SIIV when coadministered with RSVpreF or when administered alone.	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if interpretable H3N2-HAI titers cannot be obtained).	N/A

2.1.1. Primary Estimand(s)

2.1.1.1. Primary RSV Immunogenicity Estimands

The primary estimands for the RSV immunogenicity objective will use the hypothetical strategy and compare the RSVpreF immune response in participants without the intercurrent events. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed. It includes the following 5 attributes:

- **Treatment condition:** RSVpreF administered at Visit 1 in the coadministration group vs RSVpreF administered at the Month 1 visit (Visit 2) in the sequential-administration group.
- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.
- **Variables:** RSV serum NTs for subgroup A and subgroup B measured at the Month 1 visit in the coadministration group and RSV NTs for subgroup A and subgroup B measured at the Month 2 visit for the sequential-administration group.
- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not receive the study intervention as randomized.
  2. The participant did not meet the study inclusion criteria or did meet the exclusion criteria.
  3. Major protocol violations: The participant received a prohibited vaccine or treatment that may alter the immune response.
  4. Blood was taken outside an acceptable window for immunogenicity evaluation (<25 days after RSVpreF administration or >49 days after RSVpreF administration).

  The clinical question of interest is based on whether the immune response elicited from RSVpreF via coadministration with SIIV, without any influence from any other immune-modifying drugs or vaccines and measured at a homogeneous time window, is noninferior to that of RSVpreF administrated alone (ie, without SIIV). Therefore, all data after intercurrent events 1, 2, and 3, as well as all data at intercurrent event 4, if collected, will be excluded. Major protocol violations will be determined by clinical review (through the data handling memo).

- **Population-level summary**: GMR, defined as the ratio of RSV A and RSV B neutralizing GMTs between the 2 treatment groups.

2.1.1.2. Primary SIIV Immunogenicity Estimands

The primary estimands for the SIIV immunogenicity objective will use the hypothetical strategy and compare the SIIV immune response among participants without the intercurrent events. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed. It includes the following 5 attributes:

- **Treatment condition:** SIIV administered in the coadministration group vs SIIV administered in the sequential-administration group at Visit 1.
- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.
- **Variables:** Strain-specific HAI titers (or H3N2-neutralizing antibody titers if interpretable H3N2-HAI titers cannot be obtained) measured at the Month 1 visit (Visit 2).
- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not receive the study intervention as randomized.
  2. The participant did not meet the study inclusion criteria or did meet the exclusion criteria.
  3. Major protocol violations: The participant received a prohibited vaccine or treatment that may alter the immune response.
  4. Blood was taken outside an acceptable window for immunogenicity evaluation (<25 days or >49 days after SIIV administration).

  The clinical question of interest is based on whether the immune response elicited from SIIV via coadministration with RSVpreF, without any influence from any other immune-modifying drugs or vaccines and measured at a homogeneous time window, are noninferior to that of SIIV administrated alone (ie, without RSVpreF). Therefore, all data after intercurrent events 1, 2, and 3, as well as all data at intercurrent event 4, if collected, will be excluded. Major protocol violations will be determined by clinical review (through the data handling memo).

- **Population-level summary:** GMR, defined as the ratio of strain-specific HAI (or H3N2-neutralizing antibody titers if interpretable H3N2-HAI titers cannot be obtained) GMTs between the 2 treatment groups.

2.1.1.3. Primary Safety Estimands

The primary estimands for the safety objective will use the treatment policy strategy and estimate the safety rate regardless of whether an intercurrent event occurs.

Reactogenicity estimands after Vaccination 1 have the following 5 attributes:

- **Treatment condition:** RSVpreF or placebo administered at Visit 1.
- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.
- **Variables:** Each prompted item from the e-diary from Days 1 through 7 after vaccination (refer to Section 3.1.3.1, and Section 3.1.3.3).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.1.1.1 and Section 2.1.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting each prompted reactogenicity item in the RSVpreF group and the placebo group separately.

Reactogenicity estimands after Vaccination 2 have the following 5 attributes:

- **Treatment condition:** RSVpreF or placebo administered at the Month 1 visit (Visit 2).
- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.
- **Variables:** Each prompted item from the e-diary from Days 1 through 7 after vaccination (refer to Section 3.1.3.1, and Section 3.1.3.3).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.1.1.1 and Section 2.1.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting each prompted reactogenicity item in the RSVpreF group and the placebo group separately.

AE and SAE estimands after Vaccination 1 have the following 5 attributes:

- **Treatment condition:** RSVpreF or placebo administered at Visit 1.
- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.

- **Variables:** AEs reported within 1 month after Vaccination 1 (before Vaccination 2), SAEs reported within 1 month after Vaccination 1 (before Vaccination 2) (refer to Section 3.1.3.4 through Section 3.1.3.5).

- **Intercurrent events:** Some of the intercurrent events listed in Section 2.1.1.1 and Section 2.1.1.2 may apply. However, all data collected after the intercurrent event will be included.

- **Population-level summary:** The rates of reporting AEs and SAEs in the RSVpreF group and the placebo group separately.

AE and SAE estimands after Vaccination 2 have the following 5 attributes:

- **Treatment condition:** RSVpreF or placebo administered at the Month 1 visit (Visit 2).

- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.

- **Variables:** AEs reported within 1 month after Vaccination 2 and SAEs reported within 1 month after Vaccination 2 (refer to Section 3.1.3.4 through Section 3.1.3.5).

- **Intercurrent events:** Some of the intercurrent events listed in Section 2.1.1.1 and Section 2.1.1.2 may apply. However, all data collected after the intercurrent event will be included.

- **Population-level summary:** The rates of reporting AEs and SAEs in the RSVpreF group and the placebo group separately.

2.1.2. Secondary Estimand(s)

2.1.2.1. Secondary RSV Immunogenicity Estimands

The estimands for the secondary RSV immunogenicity objective will use the hypothetical strategy and estimate the RSVpreF immune response when the intercurrent event would not occur. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed.

Estimands for the secondary RSV immunogenicity objective have the following 5 attributes:

- **Treatment condition:** RSVpreF administered at Visit 1 in the coadministration group and RSVpreF administered at the Month 1 visit (Visit 2) in the sequential-administration group.

- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.

- **Variables:** RSV serum NTs for RSV A, RSV B, and RSV A and B combined (RSV A/B) before vaccination and at each applicable postvaccination blood sampling time point; RSV NT fold rise from before vaccination to each applicable postvaccination blood sampling time point for RSV A, RSV B, and RSV A/B (refer to Section 3.1.4.1 for derivation of fold rise and RSV A/B assay values).

- **Intercurrent events:** Similar to Section 2.1.1.1, all data after intercurrent events 1, 2, and 3, as well as all data at intercurrent event 4, if collected, will be excluded. Major protocol violations will be determined by clinical review (through the data handling memo).

- **Population-level summary:** The group means measured as GMTs and GMFRs for the 2 treatment groups separately.

2.1.2.2. Secondary SIIV Immunogenicity Estimands

The estimands for the secondary SIIV immunogenicity objectives will use the hypothetical strategy and estimate the SIIV immune response when the intercurrent event would not occur. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed.

Estimands for the secondary SIIV immunogenicity objective have the following 5 attributes:

- **Treatment condition:** SIIV administered at Visit 1 in the coadministration group vs SIIV administered at Visit 1 in the sequential-administration group.

- **Population:** Older adults, as defined by the study inclusion and exclusion criteria.

- **Variables:** Strain-specific HAI titers (or H3N2-neutralizing antibody titers if interpretable H3N2-HAI titers cannot be obtained) measured before SIIV vaccination and 1 month after the SIIV vaccination visit, strain-specific HAI titer (or H3N2-neutralizing antibody titers if interpretable H3N2-HAI titers cannot be obtained) fold rise from before SIIV vaccination to 1 month after SIIV vaccination.

- **Intercurrent events:** Similar to Section 2.1.1.2, all data after intercurrent events 1, 2, and 3, as well as all data at intercurrent event 4, if collected, will be excluded. Major protocol violations will be determined by clinical review (through the data handling memo).

- **Population-level summary:** The group means measured as GMTs and GMFRs for the 2 treatment groups separately.

2.1.3. Additional Estimand(s)

Additional estimands, as supplemental analyses to support the primary and secondary immunogenicity objectives, are defined. The table below lists the variables and strategies for addressing intercurrent events, which are listed in Section 2.1.1 and Section 2.1.2 for the immunogenicity objectives. The remaining 4 estimand attributes (treatment condition, variables, population, and population-level summary) are the same for each objective.

Objective	Intercurrent Events Handling Strategy
Primary RSV Immunogenicity	Treatment policy
Primary SIIV Immunogenicity	Treatment policy
Secondary RSV Immunogenicity	Treatment policy
Secondary SIIV Immunogenicity	Treatment policy

2.2. Study Design

This is a Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled study, with approximately 1400 participants to be enrolled in Australia and/or another country in the southern hemisphere.

Healthy adults ≥65 years of age will be randomized 1:1 to either the coadministration group (RSVpreF + SIIV)/placebo or the sequential-administration group (placebo + SIIV)/RSVpreF.

There are 3 scheduled study visits each 1 month apart. To assess immunogenicity, 30 mL blood will be collected prior to vaccination at Visit 1 (Day 1) and Visit 2 (Month 1), and at Visit 3 (Month 2).

Local reactions (redness, swelling, and pain at the injection site) occurring at the RSVpreF or placebo injection site (left deltoid) and systemic events (fever, headache, fatigue, nausea, vomiting, diarrhea, muscle pain, and joint pain) occurring within 7 days after each vaccination visit (Visit 1 and Visit 2) will be prompted for and collected daily by the participant in an e-diary device or smartphone app. SIIV injection site reactions will not be routinely collected in the e-diary.

AEs and SAEs will be collected from the signing of informed consent through Visit 3.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary RSV Immunogenicity Endpoints

RSV A– and RSV B–neutralizing antibody titers will be determined on sera collected at all 3 visits. Only the RSV NTs measured at the Month 1 visit in the coadministration group and RSV NTs measured at the Month 2 visit for the sequential-administration group are relevant to the primary RSV immunogenicity endpoints.

Titers above the LLOQ are considered accurate and their quantitated values will be reported. Refer to Section 5.3.2 for LLOQ details. Titers below the corresponding LLOQ, or denoted as BLQ, will be set to 0.5 × LLOQ for analysis. Missing assay results will not be imputed.

3.1.2. Primary SIIV Immunogenicity Endpoints

HAI titers to the influenza strains in the SIIV administered will be determined on sera collected at Visits 1 and 2 (prior to and 1 month after SIIV administration). H3N2-neutralizing antibody titers may be determined if the H3N2 strain in the SIIV fails to hemagglutinate or hemagglutinates via neuraminidase rather than hemagglutinin, which may invalidate the HAI assay for H3N2. Only the immunogenicity measured at Visit 2 is relevant to the primary SIIV immunogenicity endpoints.

Titers below the corresponding LLOQ, or denoted as BLQ, will be set to 0.5 × LLOQ for analysis. Missing assay results will not be imputed.

3.1.3. Primary Safety Endpoints

In general, e-diary data that are confirmed as errors will not be used for derivation or analysis. Below is a list of safety endpoints that will be derived.

- Local reactions within 7 days after Vaccination 1 (Visit 1).
- Local reactions within 7 days after Vaccination 2 (Visit 2).
- Systemic events within 7 days after Vaccination 1 (Visit 1).
- Systemic events within 7 days after Vaccination 2 (Visit 2).
- AEs within 1 month after Vaccination 1 (Visit 1).
- AEs within 1 month after Vaccination 2 (Visit 2).
- SAEs within 1 month after Vaccination 1 (Visit 1).
- SAEs within 1 month after Vaccination 2 (Visit 2).

3.1.3.1. Local Reactions Within 7 Days After Vaccination 1

The local reactions reported in the e-diary are redness, swelling, and pain at the injection site from Day 1 through Day 7 after Vaccination 1, where Day 1 is the day of vaccination with RSVpreF or placebo at Visit 1. 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 local reactions on each day.

3.1.3.1.1. Presence of Local Reactions Within 7 Days After Vaccination 1

For the summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after Vaccination 1, where Day 1 is the day of Vaccination 1, the following 2 variables are derived for each participant included in the reactogenicity subset:

1. Presence (yes or no) of each local reaction on any day (Day 1 through Day 7).

   The derivation is described in Table 3.

Table 3. Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Days 1-7)	The participant reports the reaction as "yes" on any day (Days 1-7).	The participant reports the reaction as "no" on all 7 days or as a combination of "no" and missing on all 7 days.	The participant reports the reaction as missing on all 7 days.

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

2. Presence (yes or no) of any local reaction on any day (Day 1 through Day 7).

   For any local reaction on any day, a similar definition can be applied as given in Table 4.

Table 4. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Days 1-7)	The participant reports any local reaction as "yes" on any day (Days 1-7).	The participant reports all reactions as "no" on all 7 days or as a combination of "no" and missing on all 7 days for all 3 local reactions.	The participant reports all local reactions as missing on all 7 days.

3.1.3.1.2. Maximum Severity of Local Reactions Within 7 Days After Vaccination

The grading of local reactions is listed in Table 5.

Table 5. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
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

Abbreviation: e-diary = electronic diary.

a. The maximum reaction size in measuring device units is 21 (10.5 cm). Any reaction size >21 measuring device units is recorded as a number that is >20 (eg, 21) in the e-diary.
b. 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 variables are derived for each participant included in the reactogenicity subset:

1. Maximum severity of <u>each</u> local reaction on any day (Day 1 through Day 7).

The maximum severity (highest grading) of each local reaction within 7 days after vaccination will be derived. The maximum severity will be derived as follows:

= Missing, if values are missing for all days (Days 1-7);

= 0, if the participant reports all reactions as “no” or a combination of missing and “no” for all days (Days 1-7);

= *Highest grade* (maximum severity) within 7 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 7).

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

= Missing, if values are missing for all days (Days 1-7) across all 3 local reactions;

= 0, if the participant reports all reactions as "no" or a combination of missing and "no" for all days (Days 1-7) for all individual local reactions;

= *Highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "no" for at least 1 day for at least 1 local reaction.

3.1.3.1.3. Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as the 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 participant e-diary recording period (end date collected on the CRF) unless chronicity is established.

If there is no known end date, the duration will be considered unknown and set to "missing." Participants with no reported reaction have no duration.

As there is a second vaccination at Visit 2, the date the reaction ended for Vaccination 1 should not be after the beginning of Vaccination 2. Therefore, if a reaction is ongoing at the time of Vaccination 2, the end date for the reaction after Vaccination 1 would be the date of the day before Vaccination 2, which will be used for the duration computation.

3.1.3.1.4. 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 the participants report changes in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.3.1.5. Presence of Each and Any Local Reactions on Each Day and Any Day

Presence (yes or no) of each and any local reaction on each of the 7 days (Day 1 through Day 7) follows the derivation as described in Table 6.

Table 6. Derived Variables for Each and Any Local Reaction on Each Day and Any Day

Variable	Yes (1)	No (0)	Missing (.)
Each local reaction on a specific day	The participant reports the reaction on a specific day for a specific local reaction.	The participant reports the reaction as "no" on that specific day.	The participant reports the specific local reaction as missing on that specific day.
Any local reaction on a specific day	The participant reports the reaction on a specific day for any of the 3 local reactions.	The participant reports the reactions as "no" or a combination of "no" or missing on that specific day across all 3 local reactions.	The participant reports all 3 local reactions as missing on that specific day.
Each local reaction on any day	The participant reports that local reaction on any day (Days 1-7).	The participant reports the local reaction as "no" or a combination of "no" and missing across all 7 days.	The participant reports the local reaction as missing on all 7 days.
Any local reaction on any day	The participant reports any local reaction on any day (Days 1-7).	The participant reports the reactions as "no" or missing across all 7 days and across all 3 local reactions.	The participant reports all 3 local reactions as missing on all 7 days.

3.1.3.2. Local Reactions Within 7 Days After Vaccination 2

The variables to be derived for local reactions reported in the e-diary within 7 days after Vaccination 2 is similar to that after Vaccination 1.

Day 1 is the day of vaccination with RSVpreF or placebo at Visit 2.

3.1.3.3. Systemic Events

Systemic events, including fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain, are reported via the e-diary from Day 1 through Day 7 after Vaccination 1, where Day 1 is the day of Vaccination 1 with RSVpreF or placebo, and from Day 1 through Day 7 after Vaccination 2, where Day 1 is the day of Vaccination 2 with RSVpreF or placebo. The derivations for the systemic events as described below will be handled similarly to the way local reactions are handled for the presence for each participant, severity level, duration, onset day, and systemic event on each and any day.

1. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) after Vaccination 1.

2. Presence (yes or no) of any systemic event on any day (Day 1 through Day 7) after Vaccination 1.

3. Maximum severity of each systemic event on any day (Day 1 through Day 7) after Vaccination 1.

4. Maximum severity of any systemic event on any day (Day 1 through Day 7) after Vaccination 1.
5. Duration of each systemic event after Vaccination 1.
6. Onset day of each systemic event after Vaccination 1.
7. Presence (yes or no) of each systemic event on each and any of the 7 days after Vaccination 1.
8. Presence (yes or no) of any systemic event on each and any of the 7 days after Vaccination 1.
9. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) after Vaccination 2.
10. Presence (yes or no) of any systemic event on any day (Day 1 through Day 7) after Vaccination 2.
11. Maximum severity of each systemic event on any day (Day 1 through Day 7) after Vaccination 2.
12. Maximum severity of any systemic event on any day (Day 1 through Day 7) after Vaccination 2.
13. Duration of each systemic event after Vaccination 2.
14. Onset day of each systemic event after Vaccination 2.
15. Presence (yes or no) of each systemic event on each and any of the 7 days after Vaccination 2.
16. Presence (yes or no) of any systemic event on each and any of the 7 days after Vaccination 2.

The grading scale for systemic events is provided in Table 7.

Table 7. 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 a temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. For reporting purposes, fever will be analyzed using the following temperature ranges:

- Mild (≥38.0 to 38.4°C)
- Moderate (>38.4 to 38.9°C)
- Severe (>38.9 to 40.0°C)
- Grade 4 (>40.0°C)

If a participant reports a fever (or severity of fever) by accident, the correct temperature will be transcribed in a data handling memo to be included in the analysis, and the temperature that is confirmed as incorrect will not be included in the analysis.

3.1.3.4. Adverse Events

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

The following derivations will be included for each participant:

1. Any AE reported
2. Any related AE reported
3. Any immediate AE (AE start time is within 30 minutes after vaccination)
4. Any severe AE
5. Any life-threatening AE
6. Any AE leading to study withdrawal

Each of the above will be derived for the following analysis intervals:

1. Within 1 month after Vaccination 1 (AEs starting after Vaccination 1 through Visit 2 [before Vaccination 2]).
2. Within 1 month after Vaccination 2 (AEs starting after Vaccination 2 through Visit 3 [inclusive]).

AEs starting after RSVpreF vaccination throughout the study may also be derived.

3.1.3.5. Serious Adverse Events

SAEs are collected throughout the study. The following SAE-related variables will be derived:

1. SAEs within 1 month after Vaccination 1.
2. SAEs within 1 month after Vaccination 2.

SAEs starting after RSVpreF vaccination throughout the study may also be derived.

3.1.4. Secondary Immunogenicity Endpoints

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

RSV A– and RSV B–neutralizing antibody titers will be determined at each visit.

Titers above the LLOQ are considered accurate and their quantitated values will be reported. Refer to Section 5.3.2 for LLOQ details. Titers below the corresponding LLOQ, or denoted as BLQ, will be set to 0.5 × LLOQ for analysis. Missing assay results will not be imputed.

RSV A and RSV B NTs at each blood sampling time point are included in the assay result data, thus no derivation is needed. The following variables will be derived for each participant:

1. RSV A/B at each blood sampling time point: This will be derived as the geometric mean of RSV A and RSV B NTs measured at each blood sampling time point.

2. RSV A, RSV B, and RSV A/B NT fold rise: This will be derived from before vaccination with RSVpreF to each visit after RSVpreF vaccination. The numerator is the postvaccination value and the denominator is the prevaccination value.
   For the coadministration group, assay results at Visit 1 will be used. For the sequential-administration group, assay results at Visit 2 will be used, if both Visit 1 and Visit 2 data are available; otherwise, the assay results at Visit 1 will be used, if only Visit 1 assay results are available.

When calculating a fold rise, if assay results are < LLOQ, the assay results will be converted to 0.5 × LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to LLOQ.

3.1.4.2. HAI (or H3N2-Neutralizing Antibody) Titers

HAI (or H3N2-neutralizing antibody) titers to the influenza strains in the SIIV administered will be determined on sera collected at Visits 1 and 2.

Only the fold rise on HAI (or H3N2-neutralizing antibody) titers will be derived for each influenza strain in the SIIV. Similar to NTs, when calculating a fold rise, if assay results are < LLOQ, the assay results will be converted to 0.5 × LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to LLOQ.

3.2. Other Endpoint(s)

3.2.1. Exploratory Endpoints

In addition to the endpoints included in Section 3.1.1, Section 3.1.2, and Section 3.1.4, the following variables will be derived for exploratory endpoints for each participant:

CCI [redacted]

3.2.1.2. HAI (or H3N2-Neutralizing Antibody) Titer Seroprotection

HAI seroprotection is defined as an HAI titer ≥1:40. This will be derived for each participant at Visit 1 and Visit 2.

If a meaningful HAI is not obtainable, seroprotection for H3N2 NTs will be defined as an H3N2 NT ≥1:80. Although no widely agreed cutoff protective level for NTs is available, estimates in the literature for neutralizing protective levels against H3N2 viruses range from 1:40 to 1:160. However, maximal protection against H3N2 was achieved at an HAI titer of 1:160 and an NT of 1:320, about twice as high a protective titer for H3N2 with a neutralization assay as with HAI. Considering LLOQ is the same for HAI with a neutralization assay, we chose 1:80 to define seroprotection, which is consistent with existing literature.[1,2]

3.2.1.3. HAI (or H3N2-Neutralizing Antibody) Titer Seroconversion

HAI seroconversion from before SIIV (Visit 1) to 1 month after SIIV administration (Visit 2) will be defined for each participant as follow:

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

2. If the HAI titer is ≥1:10 before SIIV administration, seroconversion is achieved if the fold rise in titer from before SIIV administration to after vaccination is ≥4.

If a meaningful HAI is not obtainable, seroconversion from before SIIV (Visit 1) to 1 month after SIIV administration (Visit 2) for H3N2 NTs will be defined as below.

3. When the NT is <1:20 before SIIV administration, seroconversion is achieved if the postvaccination NT is ≥1:80.

4. When the NT is ≥1:20 after SIIV administration, seroconversion is achieved if the fold rise in NT from before SIIV administration to after vaccination is ≥4.

3.3. Baseline Variables

3.3.1. Baseline Definition

Day 1 is defined as the day of Vaccination 1. Measurements or samples collected prior to Vaccination 1 on Day 1 are considered the baseline data for the assessments.

3.3.2. Demographics, Smoking History, and Medical History

The demographic variables that will be collected include sex, race, racial designation, 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 participant's 86th birthday, the participant is 85 years old.

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

Tobacco use is also collected at baseline.

3.3.3. E-Diary Completion

An e-diary will be considered transmitted if any data for the local reactions and systemic events are present for any day. If all data are missing for all items (local reactions and systemic events) on the e-diary for all 7 days 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.

3.3.4. Nonstudy Vaccines

Any nonstudy vaccinations received from 28 days prior to study enrollment through the conclusion of study participation will be collected.

Nonstudy vaccinations will be categorized according to the latest version (at the time of reporting) of the WHO Drug Dictionary.

3.4. Safety Endpoints

3.4.1. Adverse Events

AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (refer to Section 6.6.1).

- Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's safety review plan. As of this SAP finalization, no Tier 1 events have been identified for this vaccine.

- Tier 2 events: These are events that are not Tier 1 but are "relatively common." A MedDRA PT is defined as a Tier 2 event if its incidence is at least 1% in any vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.4.2. Vital Sign Data

The temperature collected at baseline will only be used to assess any potential protocol deviation for vaccination temporary delay. Therefore, it will not be included as a baseline variable.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants 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.

Participant Analysis Set	Description
Enrolled	All participants who have a signed ICD.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive the study intervention (RSVpreF, placebo, or SIIV).

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 or efficacy, eg, participant receipt of a prohibited vaccine or medication/treatment 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 participants with protocol violations before any analysis is carried out.

Defined Analysis Set	Description
Evaluable RSV immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Received the study interventions (RSVpreF, placebo, or SIIV) to which they were randomized at both Visit 1 and Visit 2; • Had the 1-month RSVpreF postvaccination blood collection 25 to 49 days after RSVpreF vaccination (25 days ≤ Visit 2 - Visit 1 ≤49 days for the coadministration group and 25 days ≤ Visit 3 - Visit 2 ≤49 days for the sequential-administration group); • Had no major protocol violations from randomization through the 1-month RSVpreF postvaccination blood draw; • Had at least 1 valid and determinate assay result (NT for RSV A or RSV B) 1 month after RSVpreF vaccination.
Evaluable SIIV immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Received the study interventions (RSVpreF, placebo, or SIIV) to which they were randomized in addition to SIIV at Visit 1; • Had the 1-month postvaccination blood collection 25 to 49 days after SIIV vaccination (25 days ≤ Visit 2 - Visit 1 ≤49 days); • Had no major protocol violations from randomization through the 1-month postvaccination blood draw; • Had at least 1 valid and determinate assay result (HAI titers or H3N2 NTs) 1 month after SIIV vaccination.
mITT immunogenicity population	All participants who were randomized and had at least 1 valid and determinate assay result at any time point after receiving study intervention (RSVpreF, placebo, or SIIV).

If a participant received study intervention not as randomized, the safety analysis set will be based on the vaccine group actually received and the immunogenicity analysis set will be based on the vaccine group as randomized.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Statistical Hypothesis for Primary RSV Immunogenicity

The primary immunogenicity objective on immune response elicited by RSVpreF will be evaluated by the following hypothesis for both RSV A and RSV B as measured by NT:

H_{01}: $\ln(\mu 1) - \ln(\mu 2) \leq \ln(0.667)$

where ln(0.667) corresponds to a 1.5-fold margin for noninferiority and ln(μ1) and ln(μ2) are the natural log of the geometric mean of NT at 1 month after vaccination with RSVpreF for the coadministration group (Visit 2) and the sequential-administration group (Visit 3), respectively. Noninferiority will be declared if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to sequential-administration group) is >0.667 for both RSV A and RSV B NTs.

5.1.2. Statistical Hypothesis for Primary SIIV Immunogenicity

The primary immunogenicity objective on immune response elicited by SIIV will be evaluated by the following hypothesis for each strain included in SIIV:

H_{02}: $\ln(\mu 1) - \ln(\mu 2) \leq \ln(0.667)$

where ln(0.667) corresponds to a 1.5-fold margin for noninferiority, and ln(μ1) and ln(μ2) are the natural log of the geometric mean of the strain-specific HAI titers (or H3N2-neutralizing antibody titers if interpretable H3N2-HAI titers cannot be obtained) 1 month after vaccination with SIIV for the coadministration group and the sequential-administration group, respectively. Noninferiority will be declared for an influenza strain if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to sequential-administration group) is >0.667. The primary SIIV immunogenicity objective of the study will be achieved if the noninferiority is met for each of the 4 influenza strains.

5.1.3. Multiplicity Adjustment

No multiplicity adjustment will be applied for this study. The primary objectives of noninferiority will be achieved only if the 1.5-fold equivalence criterion is met for each strain included in SIIV and for both RSV A and RSV B antigens simultaneously. Each of the 6 statistical tests (4 from the SIIV objective and 2 from the RSV objective) will use a 2-sided alpha level of 0.05.

5.2. General Methods

Unless otherwise stated, "CI" refers to a 2-sided CI in this document, either for 95% CI or Pocock-adjusted CI.

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 the difference in percentages, may also be presented, where appropriate.

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

The subsections below describe the analysis for different types of endpoints.

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 the difference in percentages, will also be presented, where applicable.

1. The 95% CI for the proportion (within–vaccine group) 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 (between–vaccine group) 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 Means

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

5.2.2.2. Geometric Mean Fold Rises

GMFRs will be calculated as the group mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. GMFRs are limited to participants with nonmissing values at both time points. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

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

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the line first going down and then to the right to the next assay value.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for 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 7-day e-diary is available, the "any day (Days 1-7)" data will be considered nonmissing.

The reactogenicity data are collected through the e-diary, which does not allow participants 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 participant on that day are nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.1. In summary, for any participant with all 7 days of the e-diary missing, this will not be included in the analysis (ie, assuming MCAR). If only 1 to 6 days of e-diary data are transferred, the reactogenicity data for the missing day(s) are considered as answering "no" for all reactions. This is based on the common assumption that no reports means no events.

Based on data from available studies, the missing data for reactogenicity are minimal, which is consistent with Li et al.[5] No sensitivity analysis is planned for reactogenicity data.

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 will be included in the final released assay data.

Values for sera that are 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, as MCAR is assumed for immunogenicity data according to Scott and Hsu.[6]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

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

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical Section 2.1.1.1).
- Analysis set: Evaluable RSV Immunogenicity population (Section 4).
- Analysis methodology: GMR, defined as the ratio of RSV A and RSV B neutralizing GMTs in the coadministration group at Visit 2 to that in the sequential-administration group at Visit 3 will be summarized along with the 95% CI (Section 5.2.2.3).
- Intercurrent events: Data collected after an intercurrent event will not be included (Section 2.1.1.1).
- Missing data: Missing data will not be imputed (Section 5.3.2).
- RSV A and RSV B neutralizing GMTs and sample size in the coadministration group at Visit 2 and that in the sequential-administration group at Visit 3 will be presented.
- GMRs and 95% CIs for the GMRs using the Student's t-distribution will be presented (Section 5.2.2.3).

- Forest plots with GMRs and the 95% CIs will be presented.

6.1.1.2. Supplementary Analyses

To support the assessment of immunogenicity, estimands as specified in Section 2.1.3 using the treatment policy strategy will be summarized with the mITT immunogenicity population using the same presentation (except the forest plots) as specified in the main analysis.

6.1.2. HAI (or H3N2-Neutralizing Antibody) Titers

6.1.2.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.1.1.2).
- Analysis set: Evaluable SIIV immunogenicity population (Section 4).
- Analysis methodology: GMR, defined as the ratio of HAI (or H3N2-neutralizing) GMTs in the coadministration group to that in the sequential-administration group for each strain contained in the SIIV, at Visit 2 will be summarized along with the 95% CI (Section 5.2.2.3).
- Intercurrent events: Data collected after an intercurrent event will not be included (Section 2.1.1.2).
- Missing data: Missing data will not be imputed (Section 5.3.2).
- HAI (or H3N2-neutralizing) GMTs and sample size in the coadministration group and that in the sequential-administration group at Visit 2 will be presented.
- GMR and 95% CI for the GMR using the Student's t-distribution will be presented (Section 5.2.2.3).
- Forest plots with GMRs and the 95% CIs will be presented.

6.1.2.2. Supplementary Analyses

To support the assessment of immunogenicity, estimands as specified in Section 2.1.3 using the treatment policy strategy will be summarized with the mITT immunogenicity population using the same presentation (except the forest plots) as specified in the main analysis.

6.1.3. Local Reactions and Systemic Events

Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after each vaccination. Participants will be summarized by vaccine group as administered at each vaccination visit.

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.1.1.3).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CIs of the proportion of participants reporting each event will use the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: All data collected are included; partially missing diary data are imputed as "no" (Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method will be presented for each vaccine group for each vaccination.
- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event throughout the 7 days will be plotted for each vaccine group for each vaccination. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.3.2. Supplementary Analysis

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.3.1, will be summarized per the supplemental analysis with the same analysis population:

- Duration (days) of each local reaction and each systemic event after each vaccination.
- Onset day of each local reaction and each systemic event after each vaccination.
- Presence of each and any local reaction and each and any systemic event, on each of the 7 days and for "any day (Days 1-7)."

The presentation of the results will include a basic descriptive summary without the 95% CIs (Section 5.2.1).

6.1.4. AEs and SAEs

Participants will be summarized by vaccine group according to the vaccine they actually received at each vaccination. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.4.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.1.1.3).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CIs of the proportion of participants reporting those events will use the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: All data collected are included.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method will be presented for each vaccine group for each analysis interval (Section 5.2.1).
- Bar charts with the proportions of participants for each variable within the specified interval will be plotted for each vaccine group for each analysis interval. The bars may be divided into relatedness categories to highlight the proportions of participants with related events.

6.1.4.2. Supplementary Analysis

To support the assessment of AEs, the endpoints below as specified in Section 3.1.3.4 and Section 3.1.3.5 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs
- Related AEs
- Severe AEs
- Life-threatening AEs
- AEs leading to withdrawal

6.2. Secondary Endpoint(s)

6.2.1. Immunogenicity as Measured by NTs

Participants will be summarized by vaccine group according to the vaccine group to which they were randomized.

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.1.2.1).

- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis methodology: 95% CIs of GMTs and GMFRs (Section 5.2.2).
- Intercurrent events and missing data: All data collected after or at intercurrent events will not be included; missing data will not be imputed.
- Descriptive statistics, including sample size (n), GMTs, GMFRs, and 95% CIs for GMTs and GMFRs will be presented for each vaccine group (Section 5.2.2).
- RCDCs for RSV A and RSV B will be plotted at 1 month after RSV vaccination, by vaccine group.

6.2.1.2. Supplementary Analysis

To support the assessment of immunogenicity, estimands as specified in Section 2.1.3 using the treatment policy strategy will be summarized with the mITT immunogenicity population using the same presentation as specified in the main analysis, without the RCDCs.

6.2.2. HAI (or H3N2-Neutralizing Antibody) Titers

The main analysis and supplemental analysis will be performed similar to NTs as described in Section 6.2.1.

6.3. Other Endpoint(s)

CCI [redacted]

6.3.2. HAI (or H3N2-Neutralizing Antibody) Titer Seroprotection

Descriptive statistics, including the proportion (%) of participants with seroprotection, the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented for each vaccine group at both Visit 1 and Visit 2, in the evaluable SIIV immunogenicity population.

6.3.3. HAI (or H3N2-Neutralizing Antibody) Titer Seroconversion

Descriptive statistics, including the proportion (%) of participants who achieved seroconversion from Visit 1 to Visit 2, the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented for each vaccine group in the evaluable SIIV immunogenicity population.

6.4. Subset Analyses

Primary immunogenicity endpoints will be analyzed by age group (65-74 years and ≥75 years of age).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

For each vaccine group, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, racial designation, and ethnicity) and tobacco use will be generated, as well as for all participants in total, based on the safety population.

Summary data may also be presented for the evaluable immunogenicity population(s) if the population size difference is >10%.

Participant data listings for demography and baseline characteristics will also be generated.

6.5.2. Study Conduct and Participant Disposition

The number and proportion of randomized participants will be included in the participant disposition summary. In addition, participants who completed each vaccination, completed the study, and withdrew before each study visit, along with the reasons for withdrawal, will be tabulated by vaccine group and for all participants included in the randomized population. The reasons for withdrawal will be those as specified in the database.

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

Standard listings will be generated, including, but not limited to, participants who withdrew during the study, participants excluded from analysis populations, and participants with major protocol violations.

6.5.3. Nonstudy Vaccines

Nonstudy vaccines recorded 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.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

For all of the AEs categorized in Section 3.1.3.4 and Section 3.1.3.5, each individual AE after Vaccination 1 and after Vaccination 2 will be categorized by MedDRA and descriptively summarized by vaccine group.

AEs are classified into 1 of 3 tiers (Section 3.4.1). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the active vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[4] method will be provided.

In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within the SOC. There are no Tier 1 events identified for this vaccine as of the date of this SAP.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

7. INTERIM ANALYSES

No interim analysis is planned.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
app	application
BLQ	below the limit of quantitation
CI	confidence interval
CRF	case report form
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition
ICD	informed consent document
CCI	[redacted]
IRT	interactive response technology
LLOQ	lower limit of quantitation
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NT	neutralizing titer
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
SAE	serious adverse event
SAP	statistical analysis plan
SIIV	seasonal inactivated influenza vaccine
SOC	system organ class
WHO	World Health Organization

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