Protocol C3671053

A PHASE 3 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN OLDER ADULTS IN KOREA

Statistical Analysis Plan
(SAP)

Version: 1

Date: 12 Aug 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 12 Aug 2024	Original 05 Apr 2024	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671053.

2.1. Modifications to the Analysis Plan Described in the Protocol

There is no change in analysis from the plan specified in the protocol.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Primary Safety	To describe the safety profile of RSVpreF when administered to Korean adults ≥60 years of age	• Local reactions (redness, swelling, and pain at the injection site) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) • AEs • SAEs • NDCMCs	In participants receiving the study intervention, the percentage of participants reporting: • Local reactions within 7 days after vaccination • Systemic events within 7 days after vaccination • AEs within 1 month after vaccination • SAEs throughout the study • NDCMCs throughout the study
Primary Immunogenicity	To describe the immune responses to RSV A and RSV B elicited by RSVpreF in Korean adults ≥60 years of age	• RSV A and RSV B serum NTs	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • GMT of NTs for RSV A and RSV B at each blood sampling visit • GMFR of NTs for RSV A and RSV B from before vaccination to 1 month after vaccination
Secondary Immunogenicity	To further describe the immune responses to RSV A and RSV B elicited by RSVpreF in Korean adults ≥60 years of age	• RSV A and RSV B serum NTs	• Seroresponse[a] rate of NTs for RSV A and RSV B at 1 month after vaccination

a. Seroresponse is defined as a postvaccination NT ≥4 times the LLOQ if the baseline titer is below the LLOQ; or a ≥4-fold rise from baseline to after vaccination if the baseline titer is ≥LLOQ.

2.2.1. Primary Estimand(s)

2.2.1.1. Immunogenicity Primary Estimand(s)

The primary estimands for the RSV immunogenicity objective will use the hypothetical strategy to describe 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 or placebo group as randomized at Visit 1.
- **Population**: Older adults in Korea, as defined by the study inclusion and exclusion criteria.
- **Variables**: RSV A and RSV B serum NTs.
- **Intercurrent events**: The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not meet the study inclusion criteria or did meet the exclusion criteria.
  2. The participant did not receive the study intervention as randomized.
  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 (<27 days or >42 days after RSVpreF administration).

  The clinical question of interest is the immune response elicited from RSVpreF, without any influence from any other immune-modifying drugs or vaccines and measured at a homogeneous time window. 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.

- **Population-level summary**: GMT of NTs before vaccination and 1 month after vaccination and GMFR of NTs from before vaccination to 1 month after vaccination, per study intervention group.

2.2.1.2. Safety Primary Estimand(s)

2.2.1.2.1. Reactogenicity Estimand(s)

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 have the following 5 attributes:

- **Treatment condition**: RSVpreF or placebo received on Day 1.
- **Population**: Participants as defined by the study inclusion/exclusion criteria.
- **Variables**: Each item included in the e-diary from Days 1 through 7 after vaccination (refer to Section 3.1.2.1).
- **Intercurrent events**: All data collected after the intercurrent events will be included.
- **Population-level summary**: The rates of reporting each reactogenicity item in each treatment/intervention condition.

2.2.1.2.2. Adverse Event Estimand(s)

The AE estimands have the same attributes (treatment condition, population, and intercurrent events) as the reactogenicity estimands (Section 2.2.1.2.1), except:

- **Variables**: Any AE reported within 1 month after vaccination (Section 3.1.2.2).
- **Population-level summary**: The rates of the variable (any AE reported within 1 month after vaccination) in each treatment condition.

2.2.1.2.3. Serious Adverse Event Estimand(s)

The SAE estimands have the same attributes (treatment condition, population, intercurrent events, and population-level summary) as the AE estimands (Section 2.2.1.2.2), except:

- **Variables**: Any SAE reported throughout the study (Section 3.1.2.2).

2.2.1.2.4. Newly Diagnosed Chronic Medical Condition Estimand(s)

The NDCMC estimands have the same attributes (treatment condition, population, intercurrent events, and population-level summary) as the AE estimands (Section 2.2.1.2.2), except:

- **Variables**: Any NDCMC reported throughout the study (Section 3.1.2.2).

2.2.2. Secondary Estimand(s)

2.2.2.1. Secondary Immunogenicity Estimand

The secondary immunogenicity estimand has the same attributes (treatment condition, population, and intercurrent events) as the primary immunogenicity estimand (Section 2.2.1.1), except:

- **Variables**: Seroresponse of NTs for RSV A and RSV B (Section 3.2).
- **Population-level summary**: Seroresponse rate for RSV A and RSV B per study intervention group at 1 month after vaccination.

2.2.3. Additional Estimand(s)

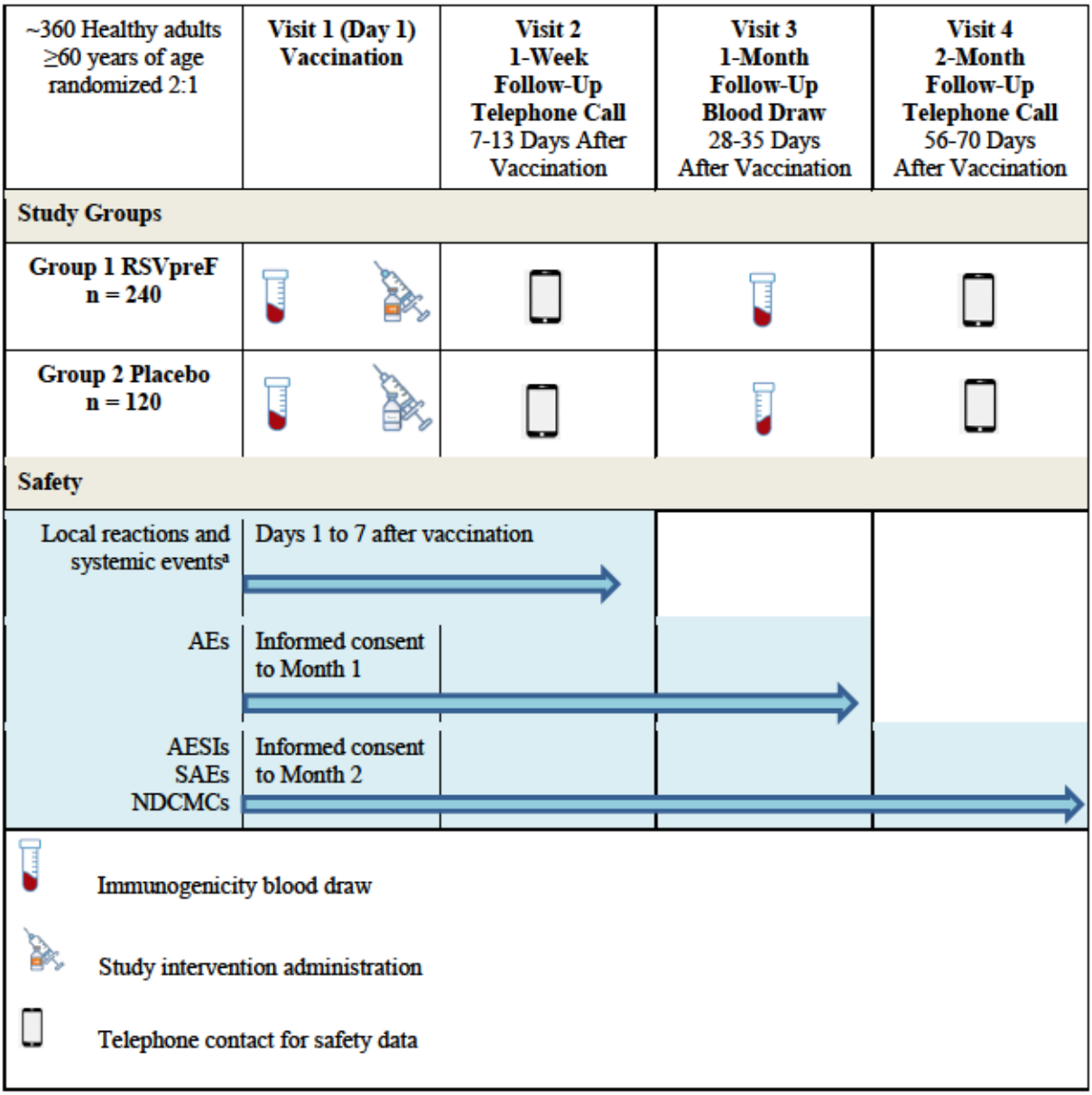
Additional estimands, as supplementary analyses to support the immunogenicity objective(s) (Section 2.2.1.1 and Section 2.2.2.1), are defined. Treatment policy will be used to address intercurrent events, which are listed in Section 2.2.1.1 for the immunogenicity objective(s). The remaining 4 estimand attributes (treatment condition, variables, population, and population-level summary) are the same.

2.3. Study Design

This is a Phase 3, randomized, double-blinded, placebo-controlled, multicenter trial to describe the safety, tolerability, and immunogenicity of bivalent RSVpreF in adults 60 years of age and older in Korea. Approximately 360 study-eligible participants will be randomized to receive either the 120-µg dose of RSVpreF or placebo in a 2:1 ratio. Randomization will be stratified by 3 age groups (60 through 69, 70 through 79, and ≥80 years), with approximately 100 participants estimated to be enrolled in the 70- through 79-year and ≥80-year age strata combined. All participants will have blood drawn at baseline prior to vaccination and at 1 month after vaccination to assess immunogenicity.

Prespecified local reaction and systemic event data will be collected in an e-diary during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). Reported Grade 3 and potential Grade 4 reactogenicity events will be assessed by the investigator or qualified person to determine unscheduled medical visit requirements.

For all participants, AEs will be collected from informed consent through 1 month following study intervention administration. SAEs, NDCMCs, and AESIs will be collected from informed consent throughout study participation.



a. Collected for 7 days, or longer for ongoing symptoms, after study intervention until symptom resolution.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Immunogenicity Primary Endpoints

RSV A– and RSV B–neutralizing antibody titers will be determined on sera collected before vaccination and at the 1-month postvaccination visit.

RSV A and RSV B serum 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 and RSV B serum NTs 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 for each participant.

2. RSV A, RSV B, and RSV A/B NT fold rise: This will be derived from NTs after vaccination to before vaccination. The numerator is the NT value 1 month after vaccination and the denominator is the NT value before vaccination.

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, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. Missing assay results will not be imputed.

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 the LLOQ.

3.1.2. Safety Primary Endpoints

Safety primary endpoints include both reactogenicity data and AEs.

The subsections below describe how to derive each safety endpoint.

3.1.2.1. Local Reactions and Systemic Events Within 7 Days After Vaccination

Reactogenicity (ie, local reactions and systemic events) will be reported via the enhanced e-diary with recalling period. Additionally, for any missed response in the e-diary or completely missing e-diary, participants will be asked by the investigator at the site visit to recall any experienced reactogenicity during the missed day(s). Temperature, size of redness, or size of swelling for those who experienced reactogenicity will all be recorded for those missing days.

Every participant who receives the study intervention will have the below variables derived:

1. Presence (yes or no) of <u>each</u> local reaction/systemic event on any day (Day 1 through Day 7):

   = Yes, if the participant reports reaction as "yes" either from the e-diary or PRR during any day of Day 1 through Day 7;

   = *No,* for the vaccinated participants who were not derived as "yes" in the above.

2. Presence (yes or no) of <u>any</u> local reaction/systemic event on any day (Day 1 through Day 7):

   = Yes, if the participant reports "yes" either from the e-diary or PRR during any day of Day 1 through Day 7 for at least 1 local reaction/systemic event;

   = *No,* for the vaccinated participants who were not derived as "yes."

3. Maximum severity of <u>each</u> local reaction/systemic event on any day (Day 1 through Day 7) after vaccination:

   = *Highest grade* (maximum severity either from the e-diary or PRR) for the specific local reaction/systemic event from Day 1 through Day 7.

   = 0, for the presence derived as "no."

4. Maximum severity of <u>any</u> local reaction/systemic event on any day (Day 1 through Day 7):

   = *Highest grade* (maximum severity either from the e-diary or PRR) for any local reaction/systemic event from Day 1 through Day 7.

   = 0, for the presence derived as "no."

5. Onset day of each local reaction/systemic event:

   The onset day is the first day of reporting any severity of the specific local reaction/systemic event, either from the e-diary or PRR.

   For the onset day of each local reaction/systemic event, if the participant reports changes in severity of the local reaction/systemic event, only the first day of reporting that specific local reaction/systemic event will be counted.

6. Duration of each local reaction/systemic event:

   The duration of each local reaction/systemic event 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 collected in the CRF.

   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.

3.1.2.2. Adverse Events and Serious Adverse Events

Standard algorithms for handling missing AE dates and missing AE severity levels will be applied as described in the Pfizer vaccine data standard rules. Completely missing AE start dates will not be imputed.

The following derivations (yes/no) will be included for each participant:

1. Any AE reported through 1 month after vaccination: If the AE started on the same day of vaccination, and the AE start time is before the vaccination time, then this AE will not be counted. Otherwise, if the AE start time is missing or after the vaccination time, the AE will be included.

2. Any related AE reported through 1 month after vaccination: This is similar to the above except only the related AE is included.

3. Any immediate AE (AE start time is within 30 minutes after vaccination) reported after vaccination: This includes only AEs that started on the same day of vaccination and with a nonmissing AE start time that is within 30 minutes after vaccination.

4. Any severe or life-threatening AE reported through 1 month after vaccination.

5. Any AE leading to study withdrawal after vaccination.

6. Any AE leading to death after vaccination.

7. Any SAE reported throughout the study.

8. Any NDCMC reported throughout the study.

9. Any AESI reported throughout the study.

3.2. Secondary Endpoint(s)

RSV seroresponse 1 month after vaccination will be defined for each participant for subgroup A and subgroup B, respectively:

- If prevaccination results are ≥ LLOQ, seroresponse is achieved if there is a ≥4-fold rise from prevaccination results.

- If prevaccination results are < LLOQ, seroresponse is achieved if the postvaccination titer is ≥4 × LLOQ.

3.3. Other Safety Endpoint(s)

3.3.1. Adverse Events

AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (refer to Section 6.3.1).

- Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's safety review plan.

  Guillain-Barré syndrome (from Day 1 through Day 43 after vaccination, where Day 1 is the vaccination day), atrial fibrillation (from Day 1 through the 1-month follow-up visit), and polyneuropathy (from Day 1 through Day 43 after vaccination, where Day 1 is the day of vaccination) have been identified as Tier 1 events for RSVpreF among the age group intended for this study. The RSV program Tier 1 list of MedDRA PTs is maintained by the safety risk lead in the CAETeLiSt and is referenced in the safety surveillance review plan for the program. The current list of Tier 1 events referenced by this study for RSVpreF should be confirmed to ensure that appropriate Tier 1 events will be used to produce final tables/graphs before conducting an analysis.

- 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 at least 4 participants in at least 1 vaccine group report the event.

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

3.3.2. Vital Sign Data

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

3.3.3. Additional Reactogenicity-Related Endpoints Collected From the CRF

Sites are expected to review the e-diary data on a daily basis. For any participants who experienced any reactogenicity during the e-diary collection period (Day 1 through Day 7), this reactogenicity will be further assessed to determine if it is immediate (within 30 minutes after vaccination); it causes any discontinuation from the study; it triggers medical attention, or it is an SAE. Therefore, additional endpoints based on these data collected from the CRF are derived as below.

- Immediate reactogenicity event.

- Reactogenicity event leading to withdrawal from the study.

- Medically attended reactogenicity event.

- Reactogenicity qualified as an SAE.

- Immediate event (including both immediate reactogenicity events and immediate AEs).

3.4. Other Endpoint(s)

Not applicable.

3.5. Baseline Variables

3.5.1. Baseline Definition

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

3.5.2. Demographics, Baseline, and Medical History

The demographic variables that will be collected include sex, race, ethnicity, tobacco use, and age at vaccination.

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

Tobacco use and prespecified existing medical conditions are collected at baseline and are categorized as the following groups of pre-existing medical conditions/tobacco use:

- Heart disease (including CHF and other heart disease);
- Lung disease (including COPD and other lung disease);
- Asthma;
- Diabetes mellitus;
- Liver disease;
- Renal disease;
- Current tobacco use (excluding past tobacco use).

3.5.3. 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) in 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.

As the enhanced e-diary allows a recalling period for participants to enter missed responses in the e-diary, the following variables will be derived:

- E-diary data transmitted on each day of Day 1 through Day 7 within 24 hours of the e-diary reporting day.
- E-diary data transmitted on any day of Day 1 through Day 7 within 24 hours of the e-diary reporting day.

- E-diary data transmitted on each day of Day 1 through Day 7 regardless of the e-diary reporting day.
- E-diary data transmitted on any day of Day 1 through Day 7 regardless of the e-diary reporting day.

3.5.4. Nonstudy Vaccines

Any nonstudy vaccinations received from 28 days prior to study intervention administration 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 WHODD.

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.

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened population	All participants who have a signed ICD in the study.
Randomized population	All screened participants who are assigned a randomization number in the IRT system in this study.
Safety population	All screened participants who receive the study intervention in the study.

Defined Analysis Set	Description
Evaluable immunogenicity population	All participants who meet the following criteria: • Are eligible for the study; • Receive the study intervention to which they were randomized; • Have the 1-month postvaccination blood collection visit within 27-42 days after vaccination; • Have at least 1 valid and determinate assay result 1 month after vaccination; • Have no major protocol violations from vaccination through the 1-month postvaccination blood draw.

Defined Analysis Set	Description
mITT immunogenicity population	All participants who were randomized and had at least 1 valid and determinate assay result after receiving the study intervention.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis for the study.

5.2. General Methods

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

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 a study intervention group) will be constructed by the Clopper-Pearson method described by Newcombe.[1] The 95% CI will be presented in terms of percentage.

2. The 95% CI for the difference in the proportions (between study intervention groups) will be computed using the Miettinen and Nurminen method.[2] The 95% CI will be presented in terms of percentage.

5.2.2. Analyses for Continuous Endpoints

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 the Student 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 Student 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 the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. 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 levels 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.

The reactogenicity data are collected in the enhanced e-diary, which allows participants to enter data later if for some reason they missed an earlier opportunity to do so. Additionally, for any e-diary entries that are out of the window to reenter the information in the e-diary recollection period, the data will be collected onsite via PRR. Therefore, it is expected very few e-diary entries would be missing.

5.3.2. Immunogenicity Data

Any assay results above the LLOQ are considered accurate, and their quantitated values will be reported. Values below the LLOQ, 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 1 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 designated as 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.[3]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Immunogenicity Primary Endpoints

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.1.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: At the end of the study.
- Intercurrent events and missing data: All data collected after or at intercurrent events will not be included (Section 2.2.1.1); missing data will not be imputed (Section 5.3).
- Analysis methodology: Descriptive statistics, including sample size (n), RSV A NTs, RSV B NTs, and RSV A/B NT GMTs and GMFRs, and the 95% CIs for GMTs and GMFRs at each applicable visit, will be presented (Section 5.2.2).
- RCDCs for RSV A and RSV B at each blood sampling time point will be plotted (Section 5.2.2.3).

6.1.1.2. Supplementary Analysis

To support the assessment of immunogenicity, supplementary analysis will be performed based on the mITT immunogenicity population using the same presentation as specified in the main analysis, except that RCDC will not be presented.

6.1.2. Local Reactions and Systemic Events

Analyses of reactogenicity endpoints are based on the safety population that includes participants with any reactogenicity data reported after vaccination. Reactogenicity data (Section 3.1.2.1) will be summarized by vaccine group according to the study intervention the participants actually received.

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.2.1).
- Analysis set: Safety population (Section 4).

- Analysis methodology: The 95% CI of the proportion of participants reporting each event will be calculated using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: At the end of the study.
- Intercurrent events and missing data: All data collected after the intercurrent events will be included.
- Descriptive statistics on each local reaction/systemic event and any local reactions/systemic events with maximum severity reported from Day 1 to Day 7, 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 group (Section 5.2.1).
- 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. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.2.2. Supplementary Analysis

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.2.1, will be summarized per the supplementary analysis with the same safety population:

- Duration (days) of each local reaction and each systemic event after vaccination.
- Onset day of each local reaction and each systemic event after vaccination.

The presentation of the results will include a basic descriptive summary without the 95% CIs for each vaccine group.

6.1.3. AEs, SAEs, and NDCMCs

AEs, SAEs, and NDCMCs will be summarized by vaccine group according to the study interventions the participants actually received. All AEs after informed consent and prior to the vaccination will not be included in the analyses but will be listed.

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.2.2, Section 2.2.1.2.3, and Section 2.2.1.2.4).
- Analysis set: Safety population (Section 4).
- Analysis timing: At the end of the study.

- Intercurrent events and missing data: All data collected after the intercurrent events will be included.
- Analysis methodology: 95% CIs of the proportion of participants reporting those events will be calculated by the Clopper-Pearson method (Section 5.2.1).
- Descriptive statistics on AEs reported through 1 month after vaccination, SAEs reported throughout the study, and NDCMCs reported throughout the study, 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 (Section 5.2.1).
- Bar charts with the proportions of participants for each variable will be plotted for each group. The bars may be divided into relatedness categories to highlight the proportions of participants with related events.

6.1.3.2. Supplementary Analysis

To support the assessment of AEs, the endpoints below, as specified in Section 3.1.2.2, will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs reported after vaccination.
- Related AEs reported through 1 month after vaccination.
- Severe or life-threatening AEs reported through 1 month after vaccination.
- AEs leading to withdrawal.
- AEs leading to death.
- AESIs.

6.2. Secondary Endpoint(s)

6.2.1. Immunogenicity Secondary Endpoint(s)

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.1.1).
- Intercurrent events and missing data: All data collected after or at intercurrent events will not be included (Section 2.2.1.1); missing data will not be imputed (Section 5.3).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: At the end of the study.

- Analysis methodology: NT seroresponse rates at 1 month after vaccination will be summarized with the proportion (%) and the numerator (n) and the denominator (N) for each group for RSV A and RSV B (Section 5.2.1).

6.2.1.2. Supplementary Analysis

To support the assessment of immunogenicity, estimands as specified in Section 2.2.3, using the treatment policy strategy, may be summarized with the mITT immunogenicity population using the same presentation as specified in the main analysis.

6.3. Other Safety Summaries and Analyses Endpoints

6.3.1. Adverse Events

For all of the AEs categorized in Section 3.1.2.2, each individual AE will be categorized by MedDRA and descriptively summarized by vaccine group.

AEs are classified into 1 of 3 tiers (Section 3.3.1). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccination group and placebo group in the percentage of participants reporting the events, based on the Miettinen and Nurminen[2] method, will be provided. In addition, for Tier 1 events, the p-values will also be presented for the difference between groups in the percentage of participants reporting the events. For Tier 3 events, counts and percentages for each vaccine group will be provided.

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.

6.3.2. Additional Reactogenicity-Related Endpoints

Descriptive statistics on immediate reactogenicity events, reactogenicity events leading to withdrawal, medically attended reactogenicity events, reactogenicity events being SAEs and immediate events will be provided, 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 group (Section 5.2.1).

6.4. Other Endpoint(s)

Not applicable.

6.5. Subset Analyses

Primary safety and immunogenicity endpoints will be analyzed by age group, as well as by tobacco use and prespecified existing medical conditions.

6.6. Baseline and Other Summaries and Analyses

For each vaccine group, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, ethnicity, and tobacco use) will be generated, as well as for all participants in total, based on the safety population. Summary data will also be presented for the evaluable and mITT immunogenicity populations.

6.6.1. Study Conduct and Participant Disposition

The number and proportion of randomized participants will be included in the participant disposition summary. In addition, vaccinated participants who completed the study, and participants who withdrew after vaccination, along with the reasons for withdrawal, will be tabulated by vaccine group and for all participants.

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

The e-diary completion rate will be summarized for the safety population, by vaccine group, and will be summarized with the categorized days specified in Section 3.5.3.

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

6.6.2. Nonstudy Vaccination

Any nonstudy vaccine used from 28 days prior to study intervention administration until the last study visit may be summarized by vaccine group and for all participants included in the safety population.

7. INTERIM ANALYSES

7.1. Introduction

7.1.1. Analysis Timing

No interim analysis is planned. One final analysis will be performed when all immunogenicity and safety data are cleaned.

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
AESI	adverse event of special interest
BLQ	below the limit of quantitation
CAETeLiSt	Custom Adverse Event Term List System
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
e-diary	electronic diary
FDA	Food and Drug Administration (United States)
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
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
NDCMC	newly diagnosed chronic medical condition
NT	neutralizing titer
PRR	patient-reported reactogenicity
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
WHODD	World Health Organization Drug Dictionary

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Signed By:	Date(GMT)	Signing Capacity
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