Protocol C3671014

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF 3 LOTS OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN HEALTHY ADULTS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 22 Feb 2022

[redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 08 Oct 2021	Original 23 Aug 2021	N/A	N/A
2/ 22 Feb 2022	Protocol amendment 1 08 Feb 2022	Sample size and lot consistency threshold modified in response to CBER feedback	• Updated Section 2.2, Section 3.5.1, Section 5.1.1, and Section 5.1.2 to match the amended protocol. • Updated Section 6.1.1.1.1 to reflect the modified lot consistency threshold. • Updated Section 6.4 to remove subgroup analysis on primary safety endpoints.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671014. 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 formal protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary CCI [redacted] objective are described in Table 2.

Table 2. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Immunogenicity		
To demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination are equivalent.	• The ratio of neutralizing GMTs obtained 1 month after vaccination for every pair of RSVpreF lots (Group 1/Group 2, Group 1/Group 3, Group 2/Group 3) for RSV A and RSV B neutralization assays, in participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable participants).	• RSV A and RSV B NTs.

Table 2. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Safety		
To evaluate the safety and tolerability profiles of 3 RSVpreF lots (Groups 1, 2, and 3).	• The incidence rate of each safety outcome in participants receiving 1 dose of the study intervention, estimated by the percentage of participants reporting the event among those who receive study intervention, in the pooled RSVpreF lots and placebo.	• 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, vomiting, nausea, diarrhea, muscle pain, and joint pain) self-reported on e-diaries for 7 days after vaccination. • AEs from the day of consent through study completion. • SAEs from the day of consent through study completion.
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2.1.1. Primary Estimands

2.1.1.1. Primary Immunogenicity Estimand

The primary immunogenicity estimand will use the hypothetical strategy and compare immune responses for 3 lots of RSVpreF 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. It includes the following 5 attributes:

- Treatment condition: RSVpreF Group 1, RSVpreF Group 2, and RSVpreF Group 3.
- Population: Healthy adults 18 through 49 years of age, inclusive, as defined by the study inclusion and exclusion criteria.
- Variables: RSV A– and RSV B–neutralizing titers measured 1 month after vaccination.
- 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/exclusion criteria.
    3. Major protocol violations – a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity.
    4. Blood was taken outside the window (<27 days or >42 days after RSVpreF administration).

The clinical question of interest is based on whether the immune responses for RSV A and RSV B induced by 3 lots of RSVpreF, without any influence from any other immune-modifying drugs or vaccines, measured at a homogeneous time point, are equivalent. Therefore, all data after intercurrent events, if applicable and collected, will be excluded. Major protocol violations will be determined by clinical review.

- Population-level summary: GMRs, defined as the ratio of RSV A–neutralizing GMTs for each between-lot comparison and the ratio of RSV B–neutralizing GMTs for each between-lot comparison (Group 1/Group 2, Group 1/Group 3, and Group 2/Group 3).

2.1.1.2. Primary Safety Estimands

The primary safety estimands will use the treatment policy strategy and variables will be estimated regardless of whether an intercurrent event occurs.

Reactogenicity estimands after vaccination include the following 5 attributes:

- Treatment condition: RSVpreF or placebo administered at Visit 1.
- Population: Healthy adults 18 through 49 years of age, inclusive, as defined by the study inclusion and exclusion criteria.
- Variables: Presence/absence and grade of any prespecified local reaction and systemic event within 7 days after vaccination.
- Intercurrent events: Some of the intercurrent events listed in Section 2.1.1.1 may apply. However, all data collected after the intercurrent event will be included.
- Population-level summary: Percentage of participants reporting prespecified local reactions and systemic events in the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo separately.

AE and SAE estimands after the day of consent have the following 5 attributes:

- Treatment condition: RSVpreF or placebo administered at Visit 1.
- Population: Healthy adults 18 through 49 years old, inclusive, as defined by the study inclusion and exclusion criteria.
- Variables: Presence/absence of AEs and SAEs reported from the day of consent through study completion (Visit 2).
- Intercurrent events: Some of the intercurrent events listed in Section 2.1.1.1 may apply. However, all data collected after the intercurrent event will be included.
- Population-level summary: Percentage of participants reporting AEs and SAEs in the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo separately.

2.1.2. Secondary Estimand(s)

Not applicable.

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Additional estimands defined for AEs and SAEs from the time of vaccination through study completion will use the treatment policy strategy and have similar attributes as the primary estimands defined for AEs and SAEs.

2.2. Study Design

This Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study will be conducted in the US. Up to 1000 healthy women and men, 18 to ≤49 years of age, will be enrolled. Allowing for a nonevaluable rate of approximately 10%, this will provide the required sample size of approximately 900 participants for the evaluable population analysis. Participants who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

There will be 4 study groups: Group 1, Group 2, Group 3 (representing 3 RSVpreF manufacturing lots), and placebo. Up to 1000 participants will be randomly assigned in a 1:1:1:1 ratio so that each group numbers approximately 250 participants.

There are 2 scheduled study visits. Participants will have blood samples for immunogenicity assessments collected both prior to vaccination (Visit 1) and 1 month after vaccination (Visit 2).

Local reactions (redness, swelling, and pain at the injection site) occurring at the RSVpreF or placebo injection site and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain) occurring within 7 days after vaccination will be prompted for and collected daily by the participant in an e-diary device or smartphone application.

AEs and SAEs will be collected from the signing of informed consent through Visit 2.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoint

- RSV A– and RSV B–neutralizing titers measured 1 month after vaccination.

3.1.2. Primary Safety Endpoints

- Local reactions self-reported on e-diaries within 7 days after vaccination.
- Systemic events self-reported on e-diaries within 7 days after vaccination.
- AEs from the day of consent through study completion.
- SAEs from the day of consent through study completion.

3.1.2.1. Local Reactions Within 7 Days After Vaccination

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, where Day 1 is the day of vaccination at Visit 1. This section describes derivations with details for the assessment of local reactions: any presence, maximum severity, duration, onset day of local reactions, and presence of local reactions on each and any day.

3.1.2.1.1. Presence of Local Reactions Within 7 Days After Vaccination

For the summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination, 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 reaction is reported as "yes" with a diameter >2.0 cm for redness/swelling or "yes" for pain on any day (Days 1-7).	The reaction is reported as "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on all 7 days or as a combination of the above 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)	Any reaction is reported as "yes" with a diameter >2.0 cm for redness/swelling or "yes" for pain on any day (Days 1-7).	All 3 local reactions are reported as "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on all 7 days or as a combination of the above and missing on all 7 days.	The participant reports all local reactions as missing on all 7 days.

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

Redness and swelling will be measured by the participant and recorded in measuring device units (range: 1 to 21 and >21; an entry in the e-diary of 21 will denote ≥21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Redness	>2.0 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	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis
Pain (at the injection site)	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale detailed in Section 10.2.3 of the protocol.

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 any 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.

3.1.2.1.3. Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction + 1). Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant 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 will not have a duration calculated.

3.1.2.1.4. 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 participant reports changes in severity of the local reaction, only the first day of reporting for that specific local reaction will be counted.

3.1.2.1.5. Presence of Local Reactions on Each 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

Variable	Yes (1)	No (0)	Missing (.)
Each local reaction on a specific day	The reaction is reported as "yes" with a diameter >2.0 cm for redness/swelling or "yes" for pain on a specific day.	The reaction is reported as "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on that specific day.	The participant reports the specific local reaction as missing on that specific day.
Any local reaction on a specific day	Any reaction is reported as redness or swelling >2.0 cm or "yes" for pain at the injection site on a specific day.	All 3 local reactions are reported as redness or swelling ≤2.0 cm and pain at the injection site as "no" on that specific day.	The participant reports all 3 local reactions as missing on that specific day.

3.1.2.2. Systemic Events Within 7 Days After Vaccination

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, where Day 1 is the day of vaccination. The derivations for the systemic events below will be handled similarly to the way local reactions are handled for any presence of systemic events, severity level, duration, onset day, and systemic events on each and any day.

1. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) after vaccination.
2. Presence (yes or no) of any systemic event on any day (Day 1 through Day 7) after vaccination.
3. Maximum severity of each systemic event on any day (Day 1 through Day 7) after vaccination.
4. Maximum severity of any systemic event on any day (Day 1 through Day 7) after vaccination.
5. Duration of each systemic event after vaccination.
6. Onset day of each systemic event after vaccination.
7. Presence (yes or no) of each systemic event on each of the 7 days after vaccination.
8. Presence (yes or no) of any systemic event on each of the 7 days after vaccination.

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. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. Grade 4 systemic events will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3 of the protocol.

Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary. For reporting purposes, fever will be analyzed using the temperature ranges in Table 8.

Table 8. Ranges for Fever

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fever	≥38.0°C to 38.4°C (100.4-101.1°F)	>38.4°C to 38.9°C (101.2-102.0°F)	>38.9°C to 40.0°C (102.1-104.0°F)	>40.0°C (>104.0°F)

a. Only an investigator or qualified designee is able to classify a participant's fever as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or contact with the participant. Grade 4 fevers will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in Section 10.2.3 of the protocol.

3.1.2.3. Adverse Events

AEs follow standard definitions as outlined in Appendix 2 of the protocol. 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, where applicable:

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 below intervals:

- From the time of consent through study completion.
- From the time of vaccination through study completion.

3.1.2.4. Serious Adverse Events

SAEs follow standard definitions as outlined in Appendix 2 of the protocol. SAEs will be derived for the below intervals:

- From the time of consent through study completion.

- From the time of vaccination through study completion.

3.2. Secondary Endpoints

Not applicable.

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3.4. Baseline Variables

3.4.1. 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.

3.4.2. Demographics and Medical History

Demographic variables collected include sex, race, ethnicity, and date of birth. Age at the time of vaccination (in years) will be derived based on birthday. For example, if the vaccination date is 1 day before the participant's 19th birthday, the participant is 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination for the age calculation. If the randomization date is also missing, then the date of the informed consent will be used for the age calculation.

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

3.4.3. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions or systemic events are present for any day. If all data are missing for all items 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.

3.4.4. Nonstudy Vaccinations and Concomitant Medications

Receipt of the following concomitant medications and vaccinations will be recorded in the CRF:

- All nonstudy vaccinations received from 28 days prior to study enrollment through the conclusion of study participation.

- The following medications, although prohibited as described in Section 6.8.1 of the protocol, will be collected from Visit 1 through the end of the study if required for medical care:
    - Immunosuppressant medications.
    - Monoclonal antibodies.
    - Systemic corticosteroids, ie, oral, IM, or IV. Topical, optic, otic, inhaled, intra-articular, or intrabursal corticosteroids will not be recorded or included.
    - Blood/plasma products or immunoglobulin.

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

3.5. Safety Endpoints

3.5.1. Adverse Events

Local reactions, systemic events, AEs, and SAEs have been described above in the Primary Safety Endpoints section.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers.

- 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 the finalization of this SAP, no Tier 1 events have been identified for this vaccine.
- Tier 2 events: These are events that are not Tier 1 but are "common." A MedDRA PT is defined as a Tier 2 event if its incidence is at least 1% in the pooled RSVpreF group or in the placebo group.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.5.2. Physical Examinations and Vital Signs

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE must be reported. Physical examination findings collected at Visit 1, if clinically significant, will be recorded on the medical history CRF.

The participant's body temperature will be assessed prior to vaccination. It will only be used to assess any potential protocol deviation for vaccination temporary delay and 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.

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to study intervention	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All participants who meet the following criteria: 1. Are eligible for the study; 2. Receive the study intervention to which they were randomized at Visit 1; 3. Have a valid and determinate immunogenicity result from the blood sample collected within 27 to 42 days after vaccination; 4. Have no major protocol violations.
mITT	All randomized participants who receive study intervention and have at least 1 valid and determinate assay result after vaccination.
Safety	All randomized participants who receive study intervention.

Major protocol violations will be determined by clinical review. A major protocol violation is a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity, eg, 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.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Statistical Hypothesis

This study has 1 primary immunogenicity objective, which is to demonstrate that the immune responses for RSV A and RSV B induced by 3 lots of RSVpreF are equivalent. The objective will be evaluated at 1 month after vaccination for RSV A and RSV B using the evaluable immunogenicity population.

The null hypothesis (H_0) for lot consistency for RSV A and RSV B is as follows:

H_0: $|\ln(\mu_1) - \ln(\mu_2)| \geq \ln(1.5)$ or $|\ln(\mu_1) - \ln(\mu_3)| \geq \ln(1.5)$ or $|\ln(\mu_2) - \ln(\mu_3)| \geq \ln(1.5)$

where ln(1.5) corresponds to a 1.5-fold equivalence margin, and ln(μ1), ln(μ2), and ln(μ3) are the natural log of the geometric mean of RSV antigen-specific NTs from participants receiving RSVpreF in Group 1, Group 2, and Group 3, respectively, measured 1 month after vaccination.

Lot consistency will be declared if the 2-sided 95% CI for the ratio of GMTs for every pair of RSVpreF lots is contained in the interval (0.667, 1.5), for both antigens simultaneously.

5.1.2. Multiplicity Adjustment

No multiplicity adjustment will be applied for this study. The primary objective of equivalence will be achieved only if the 1.5-fold equivalence criterion is met for every pair of between-lot comparisons from 3 lots and for both RSV A and RSV B antigens simultaneously. Each of the 6 statistical tests (3 pairwise comparisons between lots × 2 RSV antigens) will use a 2-sided alpha level of 0.05.

5.2. General Methods

Unless stated otherwise, "vaccine group" in this section refers to participants receiving any 1 of the 3 RSVpreF lots or placebo. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT population if there is a large enough difference in sample size between the mITT population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

The safety analyses will be based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received.

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson method).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method.[2] In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group and the pooled RSVpreF lots will be provided.

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 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.

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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 RSVpreF lots 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.

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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. No sensitivity analysis is planned for reactogenicity data.

5.3.2. Immunogenicity Data

Assay results above the 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.

LLOQ values for each assay will be included in the analysis specification once they are available.

Values for sera that are insufficient (QNS), indeterminate results, or values recorded as "not done" will be set to "missing." Additionally, any time point with no blood draws will not be included in the analysis. No imputation will be done for these missing values, as MCAR is assumed for immunogenicity data according to Scott and Hsu.[3]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoint

6.1.1.1. RSV A– and RSV B–Neutralizing Titers Measured 1 Month After Vaccination

6.1.1.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.1.1.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis methodology: GMRs of RSV A–neutralizing titers for each between-lot comparison and GMRs of RSV B–neutralizing titers for each between-lot comparison (Group 1/Group 2, Group 1/Group 3, and Group 2/Group 3) at 1 month after vaccination will be provided along with associated 2-sided 95% CIs (Section 5.2.2.3).
- Intercurrent events and missing data: Data collected after an intercurrent event will not be included. Missing data will not be imputed.
- Lot consistency will be declared if the 2-sided 95% CI for each GMR is contained in the interval (0.667, 1.5).
- A forest plot with GMRs of each between-lot comparison and the associated 95% CI for RSV A and RSV B will be presented.

6.1.1.1.2. Supplementary Analyses

The main analysis will also be performed based on the mITT population.

6.1.2. Primary Safety Endpoints

6.1.2.1. Local Reactions and Systemic Events

6.1.2.1.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.1.1.2).
- Analysis set: Safety population (Section 4).
- Analysis methodology: Descriptive summary statistics (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 error will not be used for analysis.

- Descriptive statistics for each and any local reaction and each and any systemic event throughout 7 days after vaccination will be presented for the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the associated Clopper-Pearson 95% CI.

- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event throughout 7 days after vaccination will be plotted for the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.2.1.2. Supplementary Analysis

The main analysis will also be performed for each RSVpreF lot.

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

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group and the pooled RSVpreF lots (Groups 1, 2, and 3).

The proportions of participants reporting each and any local reaction and each and any systemic event on each of the 7 days after vaccination will also be summarized.

6.1.2.2. Adverse Events

6.1.2.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.1.1.2).

- Analysis set: Safety population (Section 4).

- Analysis methodology: Descriptive summary statistics (Section 5.2.1) and an additional 3-tier approach (Section 3.5.1).

- Intercurrent events and missing data: All data collected are included. Partial AE dates will be imputed using the Pfizer standard algorithm.

- Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs, by each SOC and each PT within the SOC for the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo from the day of consent through study completion. For AEs classified as Tier 2 events, the difference in proportions and associated 2-sided 95% CI between the pooled RSVpreF groups and placebo will be presented.

6.1.2.2.2. Supplementary Analysis

To support the assessment of AEs, the endpoints below as specified in Section 3.1.2.3 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs (within the first 30 minutes after vaccination)
- Related AEs
- Severe AEs
- Life-threatening AEs
- AEs leading to withdrawal

Both the main analysis and the above supplementary analysis will also be performed for each RSVpreF lot.

All AEs after the informed consent and prior to vaccination will be listed separately. The main and supplementary analyses will also be performed from the time of vaccination through study completion.

6.1.2.3. Serious Adverse Events

6.1.2.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.1.1.2).
- Analysis set: Safety population (Section 4).
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).
- Intercurrent events and missing data: All data collected are included. Partial SAE dates will be imputed using the Pfizer standard algorithm.

- Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any SAEs, by each SOC and each PT within the SOC for the pooled RSVpreF lots (Groups 1, 2, and 3) and placebo from the day of consent through study completion.

6.1.2.3.2. Supplementary Analysis

The main analysis will also be performed for each RSVpreF lot and from the time of vaccination through study completion.

6.2. Secondary Endpoint(s)

Not applicable.

CCI

[redacted]

CCI

[redacted]

6.4. Subset Analyses

Subgroup analyses based on sex may be performed on all primary immunogenicity endpoints (as supplementary analyses).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

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

Each reported medical history term will be mapped to a SOC and PT according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized for each vaccine group and for the pooled RSVpreF lots, as well as for all participants in total, based on the safety population.

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 vaccination, completed the study, and withdrew before each study visit, along with the reasons for withdrawal, will be tabulated for each vaccine group and for the pooled RSVpreF lots as well as for all participants in total. 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.

The numbers and proportions of participants who were randomized, were vaccinated, and had blood drawn within the protocol-specified time frame, and outside the specified window, will be tabulated for each vaccine group and for the pooled RSVpreF lots as well as for all participants in total.

Participant data listings of participants who withdrew during the study will be generated. Also, data listings for participants excluded from the evaluable and mITT populations will be generated separately.

The protocol deviation listings will be generated. In addition, participants who did not receive the vaccine as randomized will be listed.

6.5.3. Transmission of E-Diaries

The numbers and percentages of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period will be summarized according to the vaccine actually received, for each vaccine group and for the pooled RSVpreF lots. The safety population will be used.

6.5.4. Nonstudy Vaccinations and Concomitant Medications

Concomitant medications recorded in the database will be categorized according to the WHO Drug Dictionary and will be descriptively summarized for each vaccine group and for the pooled RSVpreF lots, as well as for all participants in total, based on the safety population.

Nonstudy vaccinations received from 28 days prior to study enrollment through the conclusion of study participation will be summarized similarly.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

A 3-tier approach will be used to summarize AEs as described in Section 3.5.1. 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 formal interim analysis will be conducted for this study. Only 1 analysis will be performed at the completion of the study.

8. REFERENCES

1. Newcombe RG. Two-sided intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

3. Scott JA, Hsu H. Missing data issues at the FDA Center for Biologics Evaluation and Research. J Biopharm Stat. 2011;21(2):196-201.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
BLQ	below the limit of quantitation
CI	confidence interval
CRF	case report form
e-diary	electronic diary
CCI [redacted]	
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
CCI [redacted]	
IM	intramuscular
IRT	interactive response technology
IV	intravenous
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
CCI [redacted]	
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
SOC	system organ class
US	United States
WHO	World Health Organization