Protocol C3671023 – Substudy A and Substudy B

A PHASE 3 PROTOCOL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN ADULTS AT HIGH RISK OF SEVERE RSV DISEASE – SUBSTUDY A AND SUBSTUDY B

Statistical Analysis Plan
(SAP)

Version: 2

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 11 Apr 2023	Original 07 Mar 2023	N/A	N/A
2 06 Sep 2023	Protocol Amendment 1 18 Aug 2023	1. Included Tier 1 events for RSVpreF per CBER request, provided additional information on Tier 2 and Tier 3 events, and added AESI accordingly. 2. Updated data on the participants selected from C3671013 to be consistent with protocol amendment 1. 3. Clarified the subset analysis of Substudy A and Substudy B. 4. Clarified the definitions of medical history conditions and immunocompromised groups in the corresponding SAP sections. 5. Updated the main analysis and added a sensitivity analysis of the primary immunogenicity endpoints in Substudy A to be	1. Added the endpoint AESI in Section 3.1.3.3, the rationale and/or definition of Tier 1 and Tier 2 events in Section 3.5.2, and the analysis of Tier 1 events and the description of the 3-tier approach in Section 6.6.1. 2. Updated data on the participants who received RSVpreF from the immunogenicity subset of C3671013 in Section 3.1 and Section 5.1. 3. Updated Section 6.4. 4. Clarified the definitions of medical history conditions and immunocompromised groups in Section 3.4.2 and simplified Section 6.4 by referring to Section 3.4.2. 5. Analysis of covariance was added in Section 5.2.2.4; main analysis was updated and supplemental and sensitivity analysis were added in Section 6.1.1.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
		consistent with protocol amendment 1.	
		6. Updated immunogenicity analysis for Substudy A and Substudy B to be consistent with protocol amendment 1 and CBER feedback on the study.	6. Updated Section 2.2. Added seroresponse for RSV A and RSV B in Section 3.1.1, Section 3.3.1, and Section 5.1, and its analysis in Section 6.1.1 and Section 6.3.1.
		7. Based on CBER feedback and to be consistent with protocol amendment 1, updated the study sample size from 525 to 675; changed threshold for declaring noninferiority from 0.5 to 0.667, ie 2-fold to 1.5-fold.	7. Updated Section 2.3 and Section 5.1.
		8. Updated reactogenicity analysis based on CBER feedback for other vaccine program studies.	8. Updated to include both related and unrelated AEs within 7 days after vaccination for pooling with reactogenicity data in Section 3.1.3. Removed "Presence of Each and Any Local Reaction on Each Day and Any Day" in Section 3.1.3 and Section 6.1.3.2. Added e-diary completion to Section 3.4.3 and the details in Section 6.5.2.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			Clarified the applicable analysis for "safety population" and added "e-diary safety population" in Section 4. Clarified the handling of missing e-diary data in Section 5.3.1.1. In Section 6.1.3, clarified analysis of local reactions and systemic events and added sensitivity analyses of the maximum severity of reactogenicity events. Clarified analysis of AEs in Section 3.1.3 and in Section 6.1.4, and added sensitivity analyses of AEs in Section 6.1.4.
		9. Editorial updates.	9. SAP title was updated to be consistent with protocol amendment 1. Deleted "(combination group to sequential-administration group)" in Section 5.2.2.3. References and Appendix 1. List of Abbreviations were updated.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671023 – Substudy A and Substudy B.

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. 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	Objectives	Endpoints	Estimands
Substudy A Primary Safety	• To describe the safety profile of RSVpreF as measured by the percentage of participants ≥18 to <60 years of age with high-risk chronic medical conditions reporting local reactions, systemic events, AEs, and SAEs following study intervention administration.	• Local reactions (pain at the injection site, redness, and swelling). • Systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain). • AEs. • NDCMCs. • SAEs.	In participants receiving study intervention: • The proportion of participants reporting local reactions within 7 days following study intervention administration. • The proportion of participants reporting systemic events within 7 days following study intervention administration. • The proportion of participants reporting AEs through 1 month following study intervention administration. • The proportion of participants reporting NDCMCs throughout the study. • The proportion of participants reporting SAEs throughout the study.
Substudy A Primary Immunogenicity	• To demonstrate that the immune responses elicited by RSVpreF in adults ≥18 to <60 years of age with high-risk chronic medical conditions are noninferior to the immune responses in vaccinated adults ≥60 years	RSV A and RSV B serum NTs.	In participants who received RSVpreF and in compliance with the key protocol criteria (evaluable immunogenicity population): • GMT ratio (GMR), estimated by the ratio

Type	Objectives	Endpoints	Estimands
	of age in the C3671013 efficacy study.		of the GMTs for RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF in Study C3671023 participants to that in Study C3671013 adults ≥60 years of age. • Difference in seroresponse rate of RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF between participants in Study C3671023 and in Study C3671013. 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 if the baseline titer is above the LLOQ.
<u>Substudy A</u> **Secondary Immunogenicity**	• To describe the immune responses elicited by RSVpreF in adults ≥18 to <60 years of age with high-risk chronic medical conditions.	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 the postvaccination blood sampling visit.
<u>Substudy B</u> **Primary Safety**	• To describe the safety profile of RSVpreF as measured by the percentage of immunocompromised participants ≥18 years of age reporting local reactions, systemic events, AEs, and SAEs following study intervention administration.	• Local reactions (pain at the injection site, redness, and swelling). • Systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue,	In participants receiving study intervention: • The proportion of participants reporting local reactions within 7 days following each study intervention administration. • The proportion of participants reporting

Type	Objectives	Endpoints	Estimands
		muscle pain, and joint pain). • AEs. • NDCMCs. • SAEs.	systemic events within 7 days following each study intervention administration. • The proportion of participants reporting AEs through 1 month following the last dose of study intervention administration. • The proportion of participants reporting NDCMCs throughout the study. • The proportion of participants reporting SAEs throughout the study.
Substudy B Primary Immunogenicity	• To describe the immune responses elicited by RSVpreF in immunocompromised adults ≥18 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 each postvaccination blood sampling visit.

2.2.1. Primary Estimands

2.2.1.1. Substudy A Primary Immunogenicity Estimands

The primary estimands for the primary immunogenicity objective will use the hypothetical strategy and compare the RSVpreF immune response of participants in Study C3671023 Substudy A to that of the participants in the C3671013 efficacy study 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:** Randomized to RSVpreF in Substudy A and randomized to RSVpreF in the C3671013 efficacy study.
- **Population:** Participants as defined by the study inclusion/exclusion criteria for Substudy A.

- **Variables:** RSV serum NTs for subgroup A and subgroup B measured at 1 month after vaccination with RSVpreF in Substudy A.

- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not receive RSVpreF as randomized in Substudy A.

  2. The participant did not meet the inclusion criteria or did meet the exclusion criteria for Substudy A.

  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).

  The clinical question of interest is based on the comparison of the immune response elicited from RSVpreF in younger adults (≥18 to <60 years of age) from this study to that of older adults (≥60 years of age) from the C3671013 efficacy study, without any influence from any other immune-modifying drugs or vaccines and measured within 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**: Model-adjusted GMR of NT, defined as the ratio of RSV A– and RSV B–neutralizing GMTs between the 2 age groups (≥18 to <60 years of age in Study C3671023 Substudy A versus ≥60 years of age in the C3671013 efficacy study), using the ANCOVA model (Section 5.2.2.4) that includes groups (Substudy A versus C3671013) with corresponding baseline titers and sex as covariates, and the seroresponse rate difference between groups (Substudy A versus C3671013 immunogenicity subset) at 1 month after vaccination for RSV A and RSV B (Section 5.2.1).

2.2.1.2. Substudy B Primary Immunogenicity Estimands

The primary estimands for the primary immunogenicity objective will use the hypothetical strategy and evaluate the RSVpreF immune response of participants in Study C3671023 Substudy B 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 received in Substudy B.

- **Population:** Participants as defined by the study inclusion/exclusion criteria for Substudy B.

- **Variables:** RSV serum NTs for subgroup A and subgroup B measured at 1 month after each dose of RSVpreF.

- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not receive the 2 RSVpreF doses in Substudy B.

  2. The participant did not meet the study inclusion criteria or did meet the exclusion criteria for Substudy B.

  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 the second dose of RSVpreF).

  The clinical question of interest is to describe the immune response elicited from RSVpreF in immunocompromised adults (≥18 years of age) among participants from this study's Substudy B, without any influence from any other immune-modifying vaccines and measured within 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 NT before vaccination and 1 month after each dose, and GMFR of NT 1 month after each dose.

2.2.1.3. Substudy A Primary Safety Estimands

2.2.1.3.1. Reactogenicity Estimands

Reactogenicity estimands have the following 5 attributes:

- **Treatment condition:** RSVpreF or placebo received on Day 1 in Substudy A.

- **Population:** Participants as defined by the study inclusion/exclusion criteria for Substudy A.

- **Variables:** Each item included in the e-diary from Days 1 through 7 after vaccination (refer to Section 3.1.3.1 and Section 3.1.3.2).

- **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 condition.

2.2.1.3.2. AE Estimands

AE estimands have the same attributes (treatment condition, population, intercurrent events) as reactogenicity estimands (Section 2.2.1.3.1), except:

- **Variables:** Any AEs reported within 1 month after vaccination (Section 3.1.3.3).
- **Population-level summary:** The rates of reporting any AE within 1 month after vaccination.

2.2.1.3.3. SAE Estimands

SAE estimands have the same attributes (treatment condition, population, intercurrent events, population-level summary) as AE estimands (Section 2.2.1.3.2), except:

- **Variables:** Any SAEs reported throughout the study (Section 3.1.3.3).

2.2.1.3.4. NDCMC Estimands

NDCMC estimands have the same attributes (treatment condition, population, intercurrent events, population-level summary) as AE estimands (Section 2.2.1.3.2), except:

- **Variables:** Any NDCMCs reported throughout the study (Section 3.1.3.3).

2.2.1.4. Substudy B Primary Safety Estimands

2.2.1.4.1. Reactogenicity Estimands

Reactogenicity estimands have the following 5 attributes:

- **Treatment condition:** RSVpreF received in Substudy B.
- **Population:** Participants as defined by the study inclusion/exclusion criteria for Substudy B.
- **Variables:** Each item included in the e-diary from Days 1 through 7 after each dose or any dose (refer to Section 3.1.3.1 and Section 3.1.3.2).
- **Intercurrent events:** All data collected after the intercurrent events will be included.
- **Population-level summary:** The rates of reporting each reactogenicity item.

2.2.1.4.2. AE Estimands

AE estimands have the same attributes (treatment condition, population, intercurrent events, population-level summary) as reactogenicity estimands (Section 2.2.1.4.1), except:

- **Variables:** AEs reported within 1 month after each dose or any dose (Section 3.1.3.3).

2.2.1.4.3. SAE Estimands

SAE estimands have the same attributes (treatment condition, population, intercurrent events, population-level summary) as reactogenicity estimands (Section 2.2.1.4.1), except:

- **Variables:** SAEs reported throughout the study (Section 3.1.3.3).

2.2.1.4.4. NDCMC Estimands

NDCMC estimands have the same attributes (treatment condition, population, intercurrent events, population-level summary) as reactogenicity estimands (Section 2.2.1.4.1), except:

- **Variables:** NDCMCs reported throughout the study (Section 3.1.3.3).

2.2.2. Secondary Estimands

The secondary estimands for immunogenicity objectives will use the hypothetical strategy and 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.

2.2.2.1. Substudy A Secondary Immunogenicity Estimands

2.2.2.1.1. Secondary RSV NT Immunogenicity Estimands

- **Treatment condition:** Randomized to RSVpreF or placebo in Study C3671023 Substudy A.
- **Population:** Participants as defined by the study inclusion/exclusion criteria for Substudy A.
- **Variables:** RSV serum NTs for subgroup A and subgroup B measured at 1 month after vaccination with RSVpreF.
- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:
    1. The participant did not receive the vaccine as randomized in Substudy A.
    2. The participant did not meet the study inclusion criteria or did meet the exclusion criteria for Substudy A.
    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 vaccination with RSVpreF or placebo).

The clinical question of interest is the immune response elicited from RSVpreF in young adults (≥18 to <60 years of age) without any influence from any other immune-modifying drugs or vaccines and measured within 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 NT before vaccination and 1 month after vaccination, and GMFR of NT 1 month after vaccination.

2.2.3. Additional Estimands

Additional estimands, as supplemental analyses to support the primary and secondary immunogenicity objectives, are defined. The table below lists the strategies for addressing intercurrent events, which are listed in Section 2.2.1.1, Section 2.2.1.2, and Section 2.2.2 for the immunogenicity objectives. The remaining estimand attributes are the same for each objective.

Immunogenicity Objective	Intercurrent Event Handling Strategy
Substudy B primary immunogenicity	Treatment policy
Substudy A secondary immunogenicity	Treatment policy

2.3. Study Design

This is a Phase 3 study to assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults at high risk of severe RSV disease. The study will consist of 2 substudies: Substudy A and Substudy B. Each substudy design is detailed separately as follows.

Substudy A Design

This is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults ≥18 to <60 years of age considered to be at high risk of RSV disease due to certain chronic medical conditions.

Approximately 675 participants ≥18 to <60 years of age considered at high risk of RSV disease due to certain chronic medical conditions, excluding immunocompromising conditions, will be randomized to receive 1 dose of RSVpreF or placebo in a 2:1 ratio.

All participants will have blood drawn at baseline prior to vaccination and at 1 month after vaccination to assess immunogenicity. Immunogenicity elicited at 1 month after vaccination with RSVpreF in Substudy A will be bridged to the immunogenicity of participants ≥60 years of age in the C3671013 efficacy study, in which RSVpreF efficacy was demonstrated.

Local reaction and systemic event data will be collected in an e-diary for 7 days after study vaccination (Days 1 through 7, where Day 1 is the day of vaccination). Reported Grade 3 reactogenicity will be assessed by the study site to determine if an unscheduled visit is required.

For all participants, AEs will be collected from informed consent through 1 month following study intervention administration, and NDCMCs and SAEs will be collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected. AESIs will be collected throughout the study.

Substudy B Design

This is a Phase 3, single-arm, open-label, multicenter study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in immunocompromised adults.

Approximately 200 immunocompromised adults ≥18 years of age will receive 2 doses of RSVpreF with an interval of 1 month. Approximately 100 participants will be ≥60 years of age and approximately 100 participants will be ≥18 to <60 years of age. All participants will have blood drawn at baseline prior to vaccination and at 1 month after (each) vaccination to assess immunogenicity.

Local reaction and systemic event data will be collected in an e-diary for 7 days after study vaccination (Days 1 through 7, where Day 1 is the day of vaccination). Reported Grade 3 reactogenicity will be assessed by the study site to determine if an unscheduled visit is required.

For all participants, AEs will be collected from informed consent through 1 month following study intervention administration, and NDCMCs and SAEs will be collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will be collected. AESIs will be collected throughout the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Substudy A Primary Immunogenicity Endpoint

RSV A– and RSV B–neutralizing antibody titers will be determined on sera collected before vaccination and at the 1-month postvaccination visit. NT data collected from Substudy A will be concurrently tested with the sera collected from C3671013 immunogenicity subset RSVpreF recipients at both the prevaccination visit and the 1-month postvaccination 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.

In addition, RSV seroresponse 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 below LLOQ, seroresponse is achieved if the postvaccination titer is ≥4 × LLOQ.

3.1.2. Substudy B Primary Immunogenicity Endpoint

RSV A– and RSV B–neutralizing antibody titers will be determined before the first dose, before the second dose, and 1 month after the second dose for Substudy B.

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 for each participant.

2. RSV A, RSV B, and RSV A/B NT fold rise: This will be derived from before vaccination to each applicable postvaccination visit. The numerator is the postvaccination value and the denominator is the prevaccination value.

   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.

3.1.3. Primary Safety Endpoints for Substudy A and Substudy B

Primary safety endpoints include both reactogenicity data and AEs collected from the e-diary and AE CRF.

Based on feedback from the FDA on multiple vaccine programs, reactogenicity data will utilize both e-diary data (prompted local reactions and systemic events) and reactogenicity events reported in the AE CRF during the e-diary collection period. Since the AE CRF did not designate a specific page to collect reactogenicity data for an untransmitted e-diary, Pfizer has adopted a process of providing a listing of AEs reported within 7 days after vaccination to the clinical team to review and determine ("flag") which PTs should be considered reactogenicity events before the database lock. AEs reported on the same day of vaccination but missing the AE start time are defaulted to AEs reported after vaccination.

Following these review steps, those AEs reported within 7 days after vaccination that match with those flagged PTs will be considered reactogenicity data. If the same reactogenicity events are reported on the same day from both the e-diary and the AE CRF, the highest grade from the 2 data sources will be used for that specific day for analysis.

It should be noted that the data collection in the AE CRF is different from that of the e-diary:

- For redness, swelling, and fever, the measured size of redness and swelling at the injection site and temperature are recorded in the e-diary, but not in the AE CRF. As the missing e-diary entries are monitored with ongoing review of the prompted reactions reported in the AE CRF, any measurement recorded in the query response will be taken into consideration for the primary analysis using the data handling memo for analysis purposes. For the 7 days, only the maximum grading from both sources will be used for the aggregated severity analysis.

- For pain at the injection site and all other systemic events, the severity grading algorithm for the e-diary data and the AE CRF may not be the same, though Pfizer will choose the highest-severity grade.

If a participant did not have any e-diary data transferred within 7 days after vaccination, the AE CRF data in general will not be used for derivation, because this may inflate the denominator and bias the analysis, since participants who did not transfer e-diary data may be less likely to report reactogenicity. If a participant did not report any e-diary data, the participant will not be included in the analysis of reactogenicity data.

The subsections below describe how to derive each safety endpoint. Since the derivation is similar between Substudy A and Substudy B, no separate subsection is needed for each substudy.

3.1.3.1. Local Reactions Within 7 Days After Vaccination

The local reactions include redness, swelling, and pain at the injection site from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination with RSVpreF or placebo. Any reported reactogenicity events in the AE CRF during the e-diary collection period are included in the derivation discussed in the following section.

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 the presence of local reactions on each day, for each vaccine group as mentioned above.

3.1.3.1.1. 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, the following 2 variables are derived for each participant included in the reactogenicity subset:

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

2. Presence (yes or no) of each local reaction on any day (Day 1 through Day 7) for any dose. This is for Substudy B only.

The derivation is described in Table 2.

Table 2. Derived Variables for Each Local Reaction

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

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

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

2. Presence (yes or no) of any local reaction on any day (Day 1 through Day 7) for any dose. This is for Substudy B only.

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

Table 3. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Days 1-7) for each dose	The participant reports any local reaction as "yes" on any day (Days 1-7) for the dose.	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 for the dose.	The participant reports all local reactions as missing on all 7 days for the dose.
Any day (Days 1-7) for any dose (Substudy B only)	The participant reports any local reaction as "yes" on any day (Days 1-7) for any dose.	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 for any dose.	The participant reports all local reactions as missing on all 7 days for any dose.

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

The grading of local reactions is listed in Table 4.

Table 4. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	Mild grading from the e-diary per Table 1 in the protocol or mild from the AE CRF.	Moderate grading from the e-diary per Table 1 in the protocol or moderate from the AE CRF.	Severe grading from the e-diary per Table 1 in the protocol or severe from the AE CRF.	Necrosis or exfoliative dermatitis.
Swelling	Mild grading from the e-diary per Table 1 in the protocol or mild from the AE CRF.	Moderate grading from the e-diary per Table 1 in the protocol or moderate from the AE CRF.	Severe grading from the e-diary per Table 1 in the protocol or severe from the AE CRF.	Necrosis.
Pain (at the injection site)	Does not interfere with activity (mild from the e-diary or AE CRF).	Interferes with activity (moderate from the e-diary or AE CRF).	Prevents daily activity (severe from the e-diary or AE CRF).	Emergency room visit or hospitalization for severe pain at the injection site.

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 CRF 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) for <u>each</u> dose.

2. Maximum severity of <u>each</u> local reaction on any day (Day 1 through Day 7) for <u>any</u> dose. This is for Substudy B only.

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

= Missing, if values are missing for all days (Day 1 through Day 7)

= 0, if the participant reports all reactions as "no" or a combination of missing and "no" for all days (Day 1 through Day 7)

= *Highest grade* (maximum severity) within 7 days after vaccination (either from the e-diary or in the AE CRF), if the answer is not "no" for at least 1 day

For Substudy B, the maximum severity (highest grading) of each local reaction within 7 days after any dose will be derived after any RSVpreF dose and will be based on the variable of the maximum severity of each local reaction for each dose.

3. Maximum severity of any local reaction on any day (Day 1 through Day 7) for each dose.

4. Maximum severity of any local reaction on any day (Day 1 through Day 7) for any dose. This is for Substudy B only.

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

= Missing, if values are missing for all days (Day 1 through Day 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 (Day 1 through Day 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

For Substudy B, the maximum severity for any local reaction after any dose will be derived after any RSVpreF dose, based on the variable of the maximum severity for any local reaction for each dose.

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 AE CRF) or the date the event ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF) or AE stop date, whichever is longer, 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.

For Substudy B, as it includes 2 doses, the date that the reaction ended for 1 dose should not be after the subsequent dose. Therefore, if a reaction is ongoing at the time of a subsequent dose, the end date for the reaction after the previous vaccination would be the day before the subsequent dose date, 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 participant reports changes in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.3.2. Systemic Events Within 7 Days After Vaccination

Systemic events, including fever, fatigue/tiredness, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain, are reported from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination with RSVpreF or placebo. The derivations for the systemic events as described below will be handled similarly to the way that local reactions are handled for the presence for each participant, severity level, duration, onset day, and presence of 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 each dose.

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

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

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

5. Duration of each systemic event after each dose.

6. Onset day of each systemic event after each dose.

The above items 1 through 4 will also be derived for "after any dose." This is for Substudy B only.

The grading scale for systemic events is provided in the protocol. However, the derivation of severity of each systemic event on each day should be based on the maximum severity reported from the e-diary or AE CRF, if data are reported from both sources, or the e-diary alone if not reported from the AE CRF.

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°C to 38.4°C from the e-diary or mild grade from the AE CRF).
- Moderate (≥38.4°C to 38.9°C from the e-diary or moderate grade from the AE CRF).
- Severe (>38.9°C to 40.0°C from the e-diary or severe grade from the AE CRF).
- Grade 4 (>40.0°C from the e-diary or severe grade from the AE CRF, plus documented >40.0°C via CRF query or other sources).

If a participant reports a fever (or severity of fever) by mistake, 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.

3.1.3.3. Adverse Events and Serious 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. Completely missing AE start dates will not be imputed.

The following derivations will be included for each participant:

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

2. Any related AE reported through 1 month after the last vaccination – Similar to the above except only a related AE is included (but excluding related reactogenicity reported within 7 days after vaccination).

3. Any immediate AE (AE start time is within 30 minutes after vaccination) reported after each (and any, if applicable) vaccination – Only include AEs that started on the same day of the vaccination and with nonmissing AE start time that is within 30 minutes of the vaccination. If the immediate AE is a related reactogenicity event, this would not be included as an immediate AE.

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

5. Any AE leading to study withdrawal after vaccination.

6. Any NDCMC reported throughout the study.

7. Any SAE reported throughout the study (including reactogenicity reported in the AE CRF during the e-diary collection period).

8. Any AESI reported throughout the study.

Any AE reported before the first vaccination will not be included in the derivation.

Variables 1 through 5 listed above will be derived with 2 approaches: excluding any reactogenicity (but not excluding reactogenicity SAEs) reported in the AE CRF during the e-diary collection period, and with no exclusion at all.

3.2. Secondary Endpoint

3.2.1. Substudy A Secondary Immunogenicity Endpoint

RSV A– and RSV B–neutralizing antibody titers will be determined before vaccination, and at the 1-month postvaccination visit for Substudy A. The details of the secondary immunogenicity endpoint for Substudy A can refer to the primary immunogenicity endpoint for Substudy B in Section 3.1.2.

3.3. Other Endpoint

3.3.1. Substudy B Other Immunogenicity Endpoint

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

- If pre-Dose 1 results are ≥ LLOQ, seroresponse is achieved if there is a ≥4-fold rise from postdose results.
- If pre-Dose 1 results are below LLOQ, seroresponse is achieved if the postdose titer is ≥4 × LLOQ.

3.4. Baseline Variables

3.4.1. Baseline Definition

Day 1 is defined as the day of the vaccination for Substudy A and as the day of the first dose for Substudy B. Measurements or samples collected prior to the vaccination on Day 1 are considered the baseline data for the assessments.

3.4.2. Demographics, Baseline, and Medical History

The demographic variables that will be 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 60th birthday, the participant is 59 years of age.

Medical history of clinical significance will be collected and categorized according to the current version (at the time of reporting) of MedDRA. The prespecified medical conditions listed below are recorded for all participants on the CRF of the prespecified significant medical history, otherwise specified.

For Substudy A, the following will be derived:

- Resident of nursing home/long-term care facility
- Pulmonary conditions
  - COPD

  - Asthma
  - Other lung disease
- Cardiovascular conditions
  - CHF
  - CAD
  - Other heart disease
- Diabetes mellitus
- Other
  - Other metabolic disease
  - Liver disease
  - Renal disease
  - Neurologic disease
  - Hematologic disease

For Substudy B only, the following will be derived based on the CRF of participant characteristics – immunocompromised criteria:

- Having known advanced NSCLC
- Currently undergoing maintenance hemodialysis treatment secondary to end-stage renal disease
- Active immunomodulator therapy for an autoimmune inflammatory disorder at a stable dose
- Receiving an SOT at least 3 months (84 days) prior to enrollment and with no acute rejection episodes within 2 months (60 days) prior to enrollment

3.4.3. 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. The following variables will be derived:

- E-diary data transmitted on each day from Day 1 through Day 7.
- E-diary data transmitted on any day from Day 1 through Day 7.
- E-diary data transmitted on both Day 1 and Day 2.
- E-diary data transmitted from Day 1 through Day 3.
- E-diary data transmitted from Day 1 through Day 4.
- E-diary data transmitted from Day 1 through Day 5.
- E-diary data transmitted from Day 1 through Day 6.
- E-diary data transmitted for all 7 days.

3.4.4. 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 WHODrug Dictionary.

3.5. Safety Endpoints

3.5.1. Vital Sign Data

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

3.5.2. Adverse Events

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 (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. Guillain-Barre syndrome, acute polyneuropathy, atrial fibrillation (occurring from vaccination through the 1-month follow-up visit), preterm delivery (occurring from vaccination through the end of the study), preterm birth (occurring from vaccination through the end of the study), and hypertensive disorders of pregnancy (occurring from vaccination through the end of the study) will be included as the Tier 1 event analysis for RSVpreF. The derivation for Guillain-Barre syndrome and acute polyneuropathy is from Day 1 through Day 43 after vaccination (Day 1 is the vaccination day) for Substudy A and is from Day 1 of initial vaccination through Day 43 of the last vaccination for Substudy B. 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.

Note that the denominator for calculating the preterm delivery, preterm birth, and hypertensive disorders of pregnancy would be the number of pregnant women in the corresponding substudy.

- 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 any study intervention group. As there is no placebo group in Substudy B, Tier 2 event analysis is not defined for this substudy.

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

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

Participant Analysis Set	Description	Applicable Analysis
Enrolled population	All participants who have a signed ICD.	Study conduct such as participant disposition.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.	Immunogenicity analysis population disposition.
Safety population	All enrolled participants who received the study intervention. For Substudy B, the safety population will be defined for each dose as follows: • Safety population for Dose 1: The participants who received the first dose of RSVpreF. • Safety population for Dose 2: The participants who received 2 doses of RSVpreF.	AE/SAE analysis.

Participant Analysis Set	Description	Applicable Analysis
E-diary safety population	All participants who received the study intervention with at least 1 day of e-diary data transmitted. Note: If all participants have at least 1 day of e-diary data transmitted, this will be the same as the safety population. For Substudy B, the 2 doses will be as follows: The e-diary safety population for Dose 1: The participants who received the first dose of RSVpreF and have at least 1 day of e-diary data transferred during the Dose 1 e-diary collection period. The e-diary safety population for Dose 2: The participants who received 2 doses of RSVpreF and have at least 1 day of e-diary data transferred during the Dose 2 e-diary collection period.	Local reactions and systemic events analysis

Defined Analysis Set	Description	Applicable Analysis
Evaluable immunogenicity population	This population will be defined for Substudy A and Substudy B separately. For Substudy A, it includes all participants who meet the following criteria: • Are eligible for Substudy A. • Received the study interventions (RSVpreF or placebo) to which they were randomized. • Have the 1-month postvaccination blood collection 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.	Primary analysis population for immunogenicity endpoints (primary/secondary).

Defined Analysis Set	Description	Applicable Analysis
	For Substudy B, it includes all participants who meet the following criteria: • Are eligible for Substudy B. • Received 2 doses of RSVpreF. • Have the blood collection for 1 month after the last dose to be 27-42 days after the second dose of RSVpreF. • Have at least 1 valid and determinate assay result 1 month after vaccination (1 month after the second dose of RSVpreF). • Have no major protocol violations from vaccination through the 1-month postvaccination blood draw (1 month after the second dose of RSVpreF).	
mITT immunogenicity population	All participants who are randomized and have at least 1 valid and determinate assay result at any time point after receiving the study intervention.	Supplemental analysis on immunogenicity endpoints (primary/secondary).

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

For the primary immunogenicity objective of Substudy A, there are a total of 4 tests (2 for RSV A and 2 for RSV B). The primary immunogenicity objective will be evaluated by the following null hypothesis:

- H_0: $\ln(\mu_1) - \ln(\mu_2) \leq -\ln(1.5)$ or $p_1 - p_2 \leq -10\%$ vs
- H_a: $\ln(\mu_1) - \ln(\mu_2) > -\ln(1.5)$ and $p_1 - p_2 > -10\%$

where $-\ln(1.5)$ corresponds to a 1.5-fold margin for noninferiority in GMR, $\ln(\mu_1)$ is the mean of the natural logarithm-transformed serum NT at 1 month after vaccination from participants who received the same dose level of RSVpreF in this study (participants ≥18 to <60 years of age with high-risk chronic medical conditions), and $\ln(\mu_2)$ is the mean of the natural logarithm-transformed serum NT from participants who received RSVpreF in the C3671013 study immunogenicity subset (participants ≥60 years of age); -10% is a noninferiority margin for seroresponse rate, p_1 is the seroresponse rate at 1 month after vaccination from participants ≥18 to <60 years of age who received RSVpreF and are with high-risk chronic medical conditions, and p_2 is the seroresponse rate at 1 month after vaccination from participants who received RSVpreF in the C3671013 study immunogenicity subset (participants ≥60 years of age).

Seroresponse is defined as a postvaccination antibody titer ≥4 times the LLOQ for a baseline titer below the LLOQ (seronegative), or a ≥4-fold rise from baseline to after vaccination if the baseline titer is above the LLOQ (seropositive).

Noninferiority will be declared if both the null hypothesis of GMR and the null hypothesis of difference in seroresponse rates are rejected for both RSV A and RSV B serum NTs, with a type I error (2-sided) of 5%.

No multiplicity adjustment will be applied for this study because all 4 statistical hypotheses (2 endpoints for 2 RSV subgroups) must be rejected to declare noninferiority. Each of the 4 statistical tests 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 for 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 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.[1] 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.[2] 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 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 logarithm-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. Geometric Mean Ratios

The GMRs will be calculated as the mean of the difference of logarithm-transformed assay results between 2 groups and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithm-transformed assay results and exponentiating the confidence limits.

5.2.2.4. Analysis of Covariance

The ANCOVA model will use logarithmically transformed assay results 1 month after vaccination as dependent variables by controlling baseline assay results (in a logarithmic scale) and sex to compare the immune response in the current study with the reference group from C3671013. LS GMTs and LS GMRs will be calculated from the model-adjusted group means, group mean differences, and corresponding CIs on the natural log scale by exponentiating the results.

5.2.2.5. 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 the reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Day 1 through Day 7)" data will be considered nonmissing.

The reactogenicity data are mostly 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. In general, for any participant with all 7 days of the e-diary data missing, this participant will not be included in the analysis (ie, assuming MCAR). If only 1 through 6 days of e-diary data are transferred, it is expected that any missed reactogenicity events would be entered in the AE CRF if any experienced reactogenicity was not reported in the e-diary due to missed days. Therefore, the primary analysis will use reactogenicity recorded in the AE CRF to impute the partially missed e-diary data to estimate the reactogenicity rate during the e-diary collection period. The AE CRF is designed as a log page, which means only events that occurred will be recorded and events that did not occur will not be recorded. Therefore, all remaining missing days are considered as "no." This imputation can reasonably estimate the reactogenicity event rates during the e-diary collection period. However, data for the missing day(s) will not be imputed in the analysis of each specific day.

A sensitivity analysis will be planned for participants who completed the e-diary. Only participants with all 7 days of e-diary transferred data will be included in this sensitivity analysis.

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 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 Endpoints

6.1.1. Substudy A Primary Immunogenicity Endpoint

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

6.1.1.1. 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 5.3.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: With the primary analysis when all primary endpoint data are cleaned for analysis.
- Analysis methodology:
    - Model-adjusted GMR, and the corresponding 95% CI of RSV A and RSV B NTs at 1 month after vaccination with RSVpreF of participants in Study C3671023 Substudy A (≥18 to <60 years with high risk), compared to that of participants in the C3671013 efficacy study immunogenicity subset (≥60 years), will be summarized along with sample size (n) and model-adjusted LS GMTs with the 95% CI for the corresponding group, using ANCOVA model (Section 5.2.2.4) that includes groups (Substudy A versus C3671013), corresponding baseline titers, and sex as covariates.
    - NT seroresponse rates at 1 month after vaccination will be summarized with the proportion (%) and the numerator (n) and denominator (N) for each group for RSV A and RSV B. The seroresponse rate difference between groups (Substudy A versus C3671013 immunogenicity subset) will be summarized with 95% CI using the Miettinen and Nurminen method for RSV A and RSV B (Section 5.2.1).
- RCDCs for RSV A and RSV B will be plotted 1 month after RSV vaccination, by age group.

6.1.1.2. 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, without the RCDCs.

6.1.1.3. Sensitivity Analysis

RSV A NTs and RSV B NTs at 1 month after RSVpreF vaccination will be summarized with unadjusted GMTs and GMRs with the corresponding 95% CI (Section 5.2.2.1 and Section 5.2.2.3) for the evaluable immunogenicity population.

6.1.2. Substudy B Primary Immunogenicity Endpoint

RSV A– and RSV B–neutralizing antibody titers will be summarized.

6.1.2.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.1.2).
- Intercurrent events and missing data: All data collected after or at intercurrent events will not be included (Section 2.2.1.2); missing data will not be imputed (Section 5.3.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: At the final analysis.
- Analysis methodology: 95% CIs of GMTs and GMFRs (Section 5.2.2).
- Descriptive statistics, including sample size (n), RSV A NT, RSV B NT, and RSV A/B NT GMTs and GMFRs, and 95% CIs for GMTs and GMFRs at each applicable visit, will be presented (Section 5.2.2) by age group (≥18 to <60 and ≥60 years) as well as overall.
- RCDCs for RSV A and RSV B at each blood sampling time point will be plotted.

6.1.2.2. 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, without the RCDCs.

6.1.3. Local Reactions and Systemic Events

Reactogenicity data (Section 3.1.3.1 and Section 3.1.3.2) will be summarized separately for Substudy A and for Substudy B. Substudy A will be summarized for each of the 2 vaccine groups (Section 2.2.1.3.1).

For Substudy A, data will be summarized by vaccine group, according to the study interventions the participants actually received. For Substudy B, data will be summarized by age group (≥18 to <60 and ≥60 years).

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.3.1 and Section 2.2.1.4.1).
- Intercurrent events and missing data: All data collected are included; partially missing e-diary data are imputed from the AE CRF as "no" (Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.
- Analysis set: e-diary safety population (only participants with at least 1-day of e-diary data transferred are included in the calculation) (Section 4).
- Analysis methodology: 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 primary analyses (when all primary endpoint data are available).
- 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 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 group. 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 and Section 3.1.3.2, will be summarized per the supplemental 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.

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

6.1.3.3. Sensitivity Analysis

Two sensitivity analyses will be conducted:

- Maximum severity of reactogenicity is assessed for participants with all 7 days of e-diary data transmitted.
- Maximum severity of reactogenicity is also assessed using the e-diary data only. The difference between the primary analysis and this analysis will also be presented.

6.1.4. AEs, SAEs, and NDCMCs

AEs, SAEs, and NDCMCs will be summarized, separately, for Substudy A and for Substudy B. Substudy A data will be summarized for each of the 2 vaccine groups (Section 2.2.1.3.2, Section 2.2.1.3.3, and Section 2.2.1.3.4).

For Substudy A, data will be summarized by vaccine group according to the study interventions the participants actually received.

6.1.4.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.3.2, Section 2.2.1.3.3, Section 2.2.1.3.4, Section 2.2.1.4.2, Section 2.2.1.4.3, and Section 2.2.1.4.4).
- Intercurrent events and missing data: All data collected are included.
- Analysis set: Safety population (Section 4).
- Analysis timing: At primary analyses (when all primary endpoint data are available).
- Analysis methodology: 95% CIs of the proportion of participants reporting those events will use the Clopper-Pearson method (Section 5.2.1).
- 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 group. The bars may be divided into relatedness categories to highlight the proportions of participants with related events.
- The main analysis would be based on AEs excluding the reactogenicity events that were reported in the AE CRF (except for SAEs) (Section 3.1.3.3).

6.1.4.2. Supplementary Analysis

To support the assessment of AEs, the endpoints below, as specified in Section 3.1.3.3, will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs after each (and any, if applicable) vaccination
- Related AEs reported through 1 month after the last vaccination
- Severe or life-threatening AEs reported through 1 month after the last vaccination
- AEs leading to withdrawal from vaccination throughout the study

- NDCMCs reported from vaccination throughout the study
- AESIs reported from vaccination throughout the study

6.1.4.3. Sensitivity Analysis

In addition, a sensitivity analysis will be conducted by using all AEs (including reactogenicity reported in the AE CRF during the e-diary collection period).

6.2. Secondary Endpoint

6.2.1. Substudy A Secondary Immunogenicity Endpoint

RSV A– and RSV B–neutralizing antibody titers will be summarized for each of the 2 vaccine groups (Section 2.2.2.1.1).

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.2.1.1).
- Intercurrent events and missing data: All data collected after or at intercurrent events will not be included; missing data will not be imputed.
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: At primary analyses (when all primary endpoint data are available). If the 6-month postvaccination data are available after the primary analysis, the data will be summarized after the primary analysis with all-time points presented.
- Analysis methodology: 95% CIs of GMTs and GMFRs (Section 5.2.2).
- Descriptive statistics, including sample size (n), RSV A NT, RSV B NT, and RSV A/B NT GMTs and GMFRs, and 95% CIs for GMTs and GMFRs at each applicable visit, will be presented for each vaccine group (Section 5.2.2).

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, without the RCDCs.

6.3. Other Endpoint

6.3.1. Substudy B Other Immunogenicity Endpoint

The rate of RSV A NT seroresponse and the rate of RSV B NT seroresponse after each dose will be descriptively summarized for participants in Substudy B.

6.4. Subset Analyses

For Substudy A, all immunogenicity results will be summarized by age (18 through 49 years of age and 50 through 59 years of age), sex, race, ethnicity, and prespecified medical condition groups (defined in Section 3.4.2). The NT GMTs/GMFRs for these subgroup analyses will be applied to the participants who received RSVpreF.

For Substudy B, the primary endpoints will also be analyzed for the 2 age groups (≥18 to <60 years of age and ≥60 years of age). Additionally, primary immunogenicity will be summarized for each of the 4 immunocompromised groups (Section 3.4.2), and by race, ethnicity, and sex.

6.5. Baseline and Other Summaries and Analyses

Data will be summarized for Substudy A and Substudy B, separately. Substudy A data will be summarized for each of the 2 vaccine groups, and Substudy B data will be summarized for each of the 2 age groups (≥18 to <60 years of age and ≥60 years of age).

6.5.1. Baseline Summaries

For each vaccine group or each age 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. The medical conditions for Substudy A and the immunocompromised groups for Substudy B will also be summarized for the demographic characteristics. Summary data will also be presented for the evaluable immunogenicity 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, vaccinated participants who completed the 6-month follow-up visit, and who withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by vaccine group (for Substudy A) or by age group (for Substudy B) and for all participants. In addition, for Substudy B, the total number of participants vaccinated at each dose, and withdrawn after each dose, will also be tabulated. 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 e-diary completion rate will be summarized for the safety population, by vaccine group, as well as summarized with the categorized days specified in Section 3.4.3.

Standard listings will all 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 from 28 days prior to study enrollment through the end of the study will be categorized according to the WHODrug Dictionary and may be summarized by vaccine group for Substudy A and by age group for Substudy B, and for all participants 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 3.1.3.3, each individual AE will be categorized by MedDRA and descriptively summarized by vaccine group.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers (Section 3.5.2). 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 method, will be provided.[2] 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. For Substudy A, the analysis of Tier 1 events is planned for comparing the RSVpreF vaccination group and the placebo vaccination group. For Substudy B, the analysis of Tier 1 events will be compared with the background rate that had similar population characteristics, considering no placebo group was included in Substudy B.

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

7.1.1. Analysis Timing

For Substudy A, when all primary safety endpoint and primary immunogenicity endpoint data become available, it will be unblinded for the primary analysis. All safety data collected throughout the study will be cleaned, and primary and secondary immunogenicity data through 1 month after vaccination will also be cleaned and included in the analysis, with all type I error spent in this primary analysis.

For Substudy B, as it is open-label, data may be summarized on an ongoing basis for decision-making. Final analysis will be performed when all data are available and cleaned for analysis.

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
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BLQ	below the limit of quantitation
CAD	coronary artery disease
CAETeLiSt	Custom Adverse Event Term List System
CBER	Center for Biologics Evaluation and Research (United States)
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
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IRT	interactive response technology
LLOQ	lower limit of quantitation
LS	least square
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
NSCLC	non–small-cell lung cancer
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
SOC	system organ class
SOT	solid organ transplant
WHODrug Dictionary	World Health Organization Drug Dictionary

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Signed By:	Date(GMT)	Signing Capacity
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