Protocol C5401001

A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY COMBINATION VACCINE CANDIDATES IN OLDER ADULTS

Substudy A and Substudy B

Statistical Analysis Plan
(SAP)

Version: 2

Date: 14 Jul 2023

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 30 Jan 2023	Original 20 Dec 2022	N/A	N/A
2 14 Jul 2023	Protocol amendment 1 30 May 2023	To update the SAP per protocol amendment 1 by adding Substudy B	Added Substudy B and added Substudy B estimands to Table 2; Added Substudy B primary estimands to Section 2.2.2; Added Substudy B secondary estimands to Section 2.2.3; Added Substudy B additional estimands to Section 2.2.4; Added Section 2.3.2 with Substudy B study design.
		To update Section 3	Added Section 3.1.3 and Section 3.2 for Substudy B primary endpoints; Added Section 3.3 for Substudy B secondary endpoints; Added Substudy B other endpoints in Section 3.4. Updated corresponding vaccine groups in Section 3.4.
		To update Section 4	Added e-diary safety population for both Substudy A and Substudy B.
		To update Section 6	Added Section 6.1.6 for the analyses of Substudy B primary endpoints; Added Substudy B secondary endpoints in Section 6.2; Described the visit differences in Section 6.2.4 and age group differences in Section 6.3. Added Tier 1 analysis for both Substudy A and Substudy B in Section 6.5.

2. INTRODUCTION

This SAP provides the detailed methodology for the summary and statistical analyses of the data collected in Study C5401001 – 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

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

Table 2. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Substudy A			
SSA: Primary Safety	To evaluate the safety profile of combination RSVpreF + qIRV	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions within 7 days following each vaccination • Systemic events within 7 days following each vaccination • AEs within 1 month after each vaccination • SAEs throughout the study
SSA: Primary Immunogenicity	To describe the immune responses elicited by combination RSVpreF + qIRV in comparison with those elicited by RSVpreF alone	• RSV A and RSV B NTs	In participants in compliance with the key protocol criteria (evaluable participants): GMR of NTs for each RSV subgroup (A or B) 1 month after vaccination with combination RSVpreF + qIRV to that with RSVpreF alone (sequential-administration group, Visit A103)
SSA: Primary Immunogenicity	To describe the immune responses elicited by combination RSVpreF + qIRV in comparison with those elicited by qIRV alone	Strain-specific HAI titers for the current seasonal strains (2×A, 2×B) recommended by WHO for recombinant or cell-based influenza vaccines	In participants in compliance with the key protocol criteria (evaluable participants): GMR of strain-specific HAI titers 1 month after vaccination with combination RSVpreF + qIRV to that with qIRV alone (sequential-administration group, Visit A102)
SSA: Exploratory Immunogenicity	To further describe the immune responses elicited by combination RSVpreF + qIRV, by RSVpreF alone, and by qIRV alone	• RSV A and RSV B NTs • Strain-specific HAI titers	In participants in compliance with the key protocol criteria (evaluable participants): • GMTs of NTs for each RSV subgroup (A or B) at each applicable time point • GMFRs of NTs for each RSV subgroup (A or B) from before vaccination to each applicable postvaccination time point • GMTs of strain-specific HAI at each applicable time point • GMFRs of strain-specific HAI from before vaccination to each applicable postvaccination time point • The percentage of participants with strain-specific HAI titers ≥1:40 at each applicable time point • The percentage of participants achieving strain-specific HAI seroconversion[a] at each applicable postvaccination time point

Table 2. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Substudy B			
SSB: Primary Safety	To evaluate the safety profile of 2 formulations of combination RSVpreF + qIRV	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	In participants receiving the study intervention, the percentage of participants reporting: • Local reactions within 7 days following vaccination • Systemic events within 7 days following vaccination • AEs throughout the study • SAEs throughout the study
SSB: Secondary Immunogenicity	To describe the immune responses elicited by 2 formulations of combination RSVpreF + qIRV	• RSV A and RSV B NTs • Strain-specific HAI titers for the current seasonal strains (2×A, 2×B) recommended by WHO for recombinant or cell-based influenza vaccines	In participants in compliance with the key protocol criteria (evaluable participants): • GMT for each RSV subgroup (A or B) 1 month after vaccination with each formulation • GMT of HAI titers for each of the included strains 1 month after vaccination with each formulation
SSB: Exploratory Immunogenicity	To further describe the immune responses elicited by 2 formulations of combination RSVpreF + qIRV	• RSV A and RSV B NTs • Strain-specific HAI titers	In participants in compliance with the key protocol criteria (evaluable participants): • GMTs of NTs for each RSV subgroup (A or B) before vaccination • GMFRs of NTs for each RSV subgroup (A or B) from before vaccination to 1 month after vaccination • GMTs of strain-specific HAI titers before vaccination • GMFRs of strain-specific HAI titers from before vaccination to 1 month after vaccination • The percentage of participants with strain-specific HAI titers ≥1:40 at each time point • The percentage of participants achieving strain-specific HAI seroconversion[a] 1 month after vaccination

a. Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest, or an HAI titer ≥1:10 prior to vaccination with a 4-fold rise at the time point of interest.

2.2.1. SSA Primary Estimands

2.2.1.1. Primary RSV Immunogenicity Estimands

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

- **Treatment condition:** Randomized to combination RSVpreF + qIRV or RSVpreF alone.
- **Population:** Adults ≥60 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** RSV serum NTs for subgroup A and subgroup B measured at 1 month after vaccination with combination RSVpreF + qIRV (Visit A102) and at 1 month after RSVpreF alone for the sequential-administration group (Visit A103).
- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not receive the study intervention as randomized.
  2. The participant did not meet the study inclusion criteria or did meet the exclusion criteria.
  3. Major protocol violations: The participant received a prohibited vaccine or treatment that may alter the immune response.
  4. Blood was taken outside an acceptable window for immunogenicity evaluation (<27 days or >42 days after RSVpreF alone or combination RSVpreF + qIRV administration).

  The clinical question of interest is based on the comparison of the immune response elicited between combination RSVpreF + qIRV with that elicited by RSVpreF alone, 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 (through the data-handling memo).

- **Population-level summary:** GMR of NT, defined as the ratio of RSV A– and RSV B–neutralizing GMTs between the combination and RSVpreF-alone vaccine groups.

2.2.1.2. Primary HAI Immunogenicity Estimands

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

- **Treatment condition:** Randomized to combination RSVpreF + qIRV or qIRV alone.
- **Population:** Adults ≥60 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** Strain-specific HAI titers measured at 1 month after vaccination with combination RSVpreF + qIRV (Visit A102) and 1 month after qIRV alone for the sequential-administration group (Visit A102).
- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:

  1. The participant did not receive the study intervention as randomized.
  2. The participant did not meet the study inclusion criteria or did meet the exclusion criteria.
  3. Major protocol violations: The participant received a prohibited vaccine or treatment that may alter the immune response.
  4. Blood was taken outside an acceptable window for immunogenicity evaluation (<27 days or >42 days after qIRV alone or combination RSVpreF + qIRV administration).

  The clinical question of interest is based on the comparison of the immune response elicited between combination RSVpreF + qIRV with that elicited by qIRV alone, 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 (through the data-handling memo).

- **Population-level summary:** GMR, defined as the ratio of strain-specific HAI GMTs between the combination and qIRV-alone vaccine groups.

2.2.1.3. Primary Safety Estimands

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

2.2.1.3.1. Reactogenicity Estimands

Reactogenicity estimands have the following 5 attributes:

- **Treatment condition:** A total of 5 treatments applied for safety estimands: combination RSVpreF + qIRV administered at Visit A101, qIRV administered alone at Visit A101, placebo administered at Visit A102, RSVpreF administered alone at Visit A102, or qIRV administered alone at Visit A101 followed by RSVpreF administered alone at Visit A102 (qIRV/RSVpreF).
- **Population:** Adults ≥60 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** Each prompted item from the e-diary from Days 1 through 7 after vaccination for each treatment (refer to Section 3.1.3.1 and Section 3.1.3.2).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting each prompted reactogenicity item in the combination RSVpreF + qIRV group, the qIRV group, the placebo group, the RSVpreF group, and the qIRV/RSVpreF group separately (RSVpreF administered 1 month after qIRV).

2.2.1.3.2. AE Estimands

AE estimands have the following 5 attributes:

- **Treatment condition:** A total of 5 treatments applied for safety estimands: combination RSVpreF + qIRV administered at Visit A101, qIRV administered alone at Visit A101, placebo administered at Visit A102, RSVpreF administered alone at Visit A102, or qIRV administered alone at Visit A101 followed by RSVpreF administered alone at Visit A102 (qIRV/RSVpreF).
- **Population:** Adults ≥60 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** AEs reported within 1 month after vaccination (Section 3.1.3.3).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting AEs and SAEs in the combination RSVpreF + qIRV group, the qIRV group, the placebo group, the RSVpreF group, and the qIRV/RSVpreF (RSVpreF administered 1 month after qIRV) group separately.

2.2.1.3.3. SAE Estimands

SAE estimands have the following 5 attributes:

- **Treatment condition:** A total of 2 treatments applied for safety estimands: combination RSVpreF + qIRV administered at Visit A101, and qIRV alone for the sequential-administration group at Visit A101.
- **Population:** Adults ≥60 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** SAEs reported throughout the study (Section 3.1.3.4).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting SAEs in the combination RSVpreF + qIRV group (Group 1) and qIRV alone for the sequential-administration group (Group 2) separately.

2.2.2. SSB Primary Estimands

2.2.2.1. Primary Safety Estimands

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

2.2.2.1.1. Reactogenicity Estimands

Reactogenicity estimands have the following 5 attributes:

- **Treatment condition:** 2 treatments applied: Combination (RSVpreF + qIRV) 1.0-mL and combination (RSVpreF + qIRV) 0.5-mL at Visit B101.
- **Population:** Adults ≥50 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** Each prompted item from the e-diary from Days 1 through 7 after vaccination for each treatment (refer to Section 3.1.3.1 and Section 3.1.3.2).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting each prompted reactogenicity item in the combination (RSVpreF + qIRV) 1.0-mL group for 50-64 years, 65+ years, and 50+ years; and combination (RSVpreF + qIRV) 0.5-mL group for 50-64 years, 65+ years, and 50+ years separately.

2.2.2.1.2. AE Estimands

AE estimands have the following 5 attributes:

- **Treatment condition:** 2 treatments applied: Combination (RSVpreF + qIRV) 1.0-mL and combination (RSVpreF + qIRV) 0.5-mL at Visit B101.
- **Population:** Adults ≥50 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** AEs reported throughout the study (Section 3.1.3.3).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting AEs and SAEs in the combination RSVpreF + qIRV 1.0-mL group for 50-64 years, 65+ years and 50+ years; and combination (RSVpreF + qIRV) 0.5-mL group for 50-64 years, 65+ years and 50+ years separately.

2.2.2.1.3. SAE Estimands

SAE estimands have the following 5 attributes:

- **Treatment condition:** 2 treatments applied: Combination (RSVpreF + qIRV) 1.0-mL and combination (RSVpreF + qIRV) 0.5-mL at Visit B101.
- **Population:** Adults ≥50 years of age, as defined by the study inclusion and exclusion criteria.
- **Variables:** SAEs reported throughout the study (Section 3.1.3.4).
- **Intercurrent events:** Some of the intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 may apply. However, all data collected after the intercurrent event will be included.
- **Population-level summary:** The rates of reporting SAEs in the combination RSVpreF + qIRV 1.0-mL group for 50-64 years, 65+ years and 50+ years; and combination (RSVpreF + qIRV) 0.5-mL group for 50-64 years, 65+ years and 50+ years separately.

2.2.3. SSB Secondary Estimands

2.2.3.1. SSB Secondary Immunogenicity Estimands

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

- **Treatment condition:** 2 treatments applied: Combination (RSVpreF + qIRV) 1.0-mL and combination (RSVpreF + qIRV) 0.5-mL at Visit B101.

- **Population:** Adults ≥50 years of age, as defined by the study inclusion and exclusion criteria.

- **Variables:** RSV serum NTs and strain-specific HAI titers measured at 1 month after vaccination with combination (RSVpreF + qIRV) 1.0-mL at Visit B102 and 1 month after vaccination with combination (RSVpreF + qIRV) 0.5-mL at Visit B102.

- **Intercurrent events:** The intercurrent events listed in Section 2.2.1.1 and Section 2.2.1.2 could impact the interpretation or the measurement of the immune response.

  The clinical question of interest is based on the comparison of the immune response elicited between combination (RSVpreF + qIRV) 1.0-mL group and 0.5-mL group, 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 (through the data-handling memo).

- **Population-level summary:** The group means measured as GMTs for each RSV subgroup (A or B) and GMT of HAI titers of each strain, for the combination RSVpreF + qIRV 1.0-mL group for 50-64 years, 65+ years and 50+ years; and combination (RSVpreF + qIRV) 0.5-mL group for 50-64 years, 65+ years and 50+ years separately.

2.2.4. Additional Estimands

Additional estimands, as supplemental analyses to support the primary and secondary immunogenicity objectives, are defined in Table 2. The table below lists the variables and strategies for addressing intercurrent events, which are listed in Section 2.2.1.1 and Section 2.2.1.2, for the immunogenicity objectives. The remaining 3 estimand attributes — treatment condition, population, and population-level summary — are the same for each objective.

Objective	Variables	Intercurrent Events Handling Strategy
SSA: Primary RSV Immunogenicity	RSV serum NTs for subgroup A and subgroup B measured at 1 month after vaccination with combination RSVpreF + qIRV (Visit A102) and at 1 month after RSVpreF alone for the sequential-administration group (Visit A103).	Treatment policy
SSA: Primary HAI Immunogenicity	Strain-specific HAI titers measured at 1 month after vaccination with combination RSVpreF + qIRV (Visit A102) and 1 month after qIRV alone for the sequential-administration group (Visit A102).	Treatment policy
SSB: Secondary Immunogenicity	RSV serum NTs for subgroup A and subgroup B and strain-specific HAI titers, measured at 1 month after vaccination with (RSVpreF + qIRV) 1.0-mL or with (RSVpreF + qIRV) 0.5-mL (Visit B102).	Treatment policy

2.3. Study Design

2.3.1. Substudy A

This is a Phase 1b, parallel-group, randomized, placebo-controlled, observer-blinded substudy. Approximately 250 healthy adults ≥60 years of age will be randomized 1:1 to either:

- Group 1: combination (RSVpreF + qIRV) (Visit A101) followed by placebo (Visit A102) or
- Group 2: sequential administration of qIRV (Visit A101) followed by RSVpreF (Visit A102) administered 1 month apart.

Randomization will be stratified by 3 age groups (60 to 64, 65 to 79, and ≥80 years) within each study site. There are 3 scheduled study visits each 1 month apart. To assess immunogenicity, blood samples will be collected prior to vaccination at Visit A101 (Day 1) and Visit A102 (Month 1), and at Visit A103 (Month 2).

Local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, headache, fatigue, nausea, vomiting, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain) occurring within 7 days after each vaccination visit (Visit A101 and Visit A102) will be recorded in an e-diary device or smartphone app.

AEs and SAEs will be collected from the signing of the informed consent through Visit A103.

2.3.2. Substudy B

Substudy B is designed to evaluate the safety, tolerability, and immunogenicity of RSVpreF and a modified RNA vaccine (qIRV) against RSV and influenza when administered as a combined vaccine in a 1.0-mL formulation and a 0.5-mL formulation.

This 2-visit study will be conducted as a Phase 1b, parallel-group, randomized, placebo-controlled, observer-blinded substudy.

Approximately 200 healthy participants (n=100 per group) will be enrolled in Substudy B.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.

Healthy adults ≥ 50 years of age will be randomized 1:1 to either:

- Group 1: combination (RSVpreF + qIRV) 1.0-mL formulation or
- Group 2: combination (RSVpreF + qIRV) 0.5-mL formulation.

Participants will be randomized by age/sex strata. Randomization will be stratified at the study site by 6 age/sex groups so that approximately 100 participants will be 50 through 64 years of age and 100 will be ≥65 years of age, in addition to having balanced sex distribution between vaccine groups. These groups are as follows:

- Females 50 through 64 years of age
- Females 65 through 79 years of age
- Females ≥80 years of age
- Males 50 through 64 years of age
- Males 65 through 79 years of age
- Males ≥80 years of age

Blood will be collected prior to vaccination and at the final study visit.

Local reactions and systemic events occurring within 7 days after vaccination will be recorded in an e-diary device or smartphone application.

AEs and SAEs will be collected from the signing of informed consent through study completion.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. SSA Primary Endpoint(s)

3.1.1. Primary RSV Immunogenicity Endpoints

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

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

3.1.2. Primary HAI Immunogenicity Endpoints

HAI titers to the influenza strains will be determined on sera collected at the first 2 visits, but only the immunogenicity results for HAI measured in the combination (RSVpreF + qIRV) group, and in the sequential-administration qIRV group at the Month 1 visit, are relevant to the primary HAI immunogenicity endpoints.

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

3.1.3. Primary Safety Endpoints

In general, e-diary data that are confirmed as errors will not be used for derivation or analysis.

Feedback was received from the FDA on reactogenicity data collection and analysis. Most recently, the FDA stated the concern of missing e-diary entries for reactogenicity events. However, Pfizer sends reminders to sites to follow up on missing e-diary entries, and the reminders are also sent to sites from the vendor. Also, CRF completion guidelines do allow sites to enter e-diary events into the AE CRF. Therefore, Pfizer uses both sources for the reactogenicity data: the e-diary and the AE CRF. Since the AE CRF did not designate a specific page to collect reactogenicity data that were missing in the 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/query the AEs, and to finalize the PTs that should be considered reactogenicity before the database lock. For the AEs reported on the same day of vaccination but missing the AE start time, these AEs are defaulted to be considered AEs after vaccination. Then any AEs reported within 7 days after vaccination that match with those flagged PTs, (either "related," or unrelated as assessed by the investigator) will be pooled with reactogenicity data from the e-diary. If the same reactogenicity is 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.

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. Therefore, the maximum grading for the 3 items reported in the e-diary will be based on actual size and the FDA toxicity grading scale, but the maximum grading of the 3 reactogenicity terms from the AE CRF will be based on the grading scale on the CRF page. For the 7 days, only the maximum grading from both sources will be used for the aggregated severity analysis, though the grading algorithm is different between the 2 data sources.

- 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, the AE CRF data will not be used for derivation because the analysis of reactogenicity will be based on e-diary safety population, which is only restricted to participants who have at least 1 day of e-diary data entered. In other words, if a participant did not report any e-diary data, the participant will not be included in the analysis of reactogenicity data.

The table below lists safety endpoints that will be derived for each vaccine group.

Safety Endpoints	**Vaccine Group (as Received)**				
	Combination: RSVpreF + qIRV	**Sequential Administration: qIRV/RSVpreF**	**qIRV Alone**	**RSVpreF Alone**	**Placebo Only**
Local reactions within 7 days after vaccination	Local reactions reported within 7 days after Vaccination 1 among participants who received the combination vaccine at Visit A101 with at least 1 day of e-diary data transferred following the vaccination.	Local reactions reported within 7 days after Vaccination 1 or after Vaccination 2 among participants who received qIRV at Visit A101 with at least 1 day of e-diary transferred following the vaccination and received RSVpreF at Visit A102 with at least 1 day of e-diary data transferred following the vaccination.	Local reactions reported within 7 days after Vaccination 1 among participants who received qIRV at Visit A101 with at least 1 day of e-diary data transferred following the vaccination.	Local reactions reported within 7 days after Vaccination 2 among participants who received RSVpreF at Visit A102 with at least 1 day of e-diary data transferred following the vaccination.	Local reactions reported within 7 days after Vaccination 2 among participants who received placebo only at Visit A102 with at least 1 day of e-diary data transferred following the vaccination.

Safety Endpoints	Vaccine Group (as Received)				
	Combination: RSVpreF + qIRV	**Sequential Administration: qIRV/RSVpreF**	**qIRV Alone**	**RSVpreF Alone**	**Placebo Only**
Systemic events within 7 days after vaccination	Systemic events reported within 7 days after Vaccination 1 among participants who received the combination vaccine at Visit A101 with at least 1 day of e-diary data transferred following the vaccination.	Systemic events reported within 7 days after Vaccination 1 or after Vaccination 2 among participants who received qIRV at Visit A101 with at least 1 day of e-diary data transferred following vaccination and received RSVpreF at Visit A102 with at least 1 day of e-diary data transferred following vaccination.	Systemic events reported within 7 days after Vaccination 1 among participants who received qIRV at Visit A101 with at least 1 day of e-diary data transferred following the vaccination.	Systemic events reported within 7 days after Vaccination 2 among participants who received RSVpreF at Visit A102 with at least 1 day of e-diary data transferred following the vaccination.	Systemic events reported within 7 days after Vaccination 2 among participants who received placebo only at Visit A102 with at least 1 day of e-diary data transferred following the vaccination.
AEs within 1 month after vaccination	AEs reported from Vaccination 1 to before Vaccination 2 among participants who received the combination at Visit A101.	AEs reported from Vaccination 1 throughout the study among participants who received qIRV at Visit A101 and RSVpreF at Visit A102.	AEs reported from Vaccination 1 to before Vaccination 2 among participants who received qIRV at Visit A101.	AEs reported from Vaccination 2 through the end of the study among participants who received RSVpreF at Visit A102.	AEs reported from Vaccination 2 through the end of the study among participants who received placebo only at Visit A102.
SAEs throughout the study	SAEs reported from Vaccination 1 throughout the study among participants who received the combination at Visit A101.	SAEs reported from Vaccination 1 throughout the study among participants who received qIRV at Visit A101.	N/A	N/A	N/A

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 combination RSVpreF + qIRV, qIRV, RSVpreF, or placebo.

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 of the 5 vaccine groups 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, where Day 1 is the day of Vaccination 1 or Vaccination 2, the following 2 variables are derived for each participant included in the reactogenicity subset:

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

   The derivation is described in Table 3.

Table 3. Derived Variables for Each Local Reaction

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

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

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

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

Table 4. Derived Variables for Any Local Reaction

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

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

The grading of local reactions is listed in Table 5.

Table 5. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units from the e-diary) or mild from the AE CRF.	>5.0 cm to 10.0 cm (11 to 20 measuring device units from the e-diary) or moderate from the AE CRF.	>10 cm (>20 measuring device units from the e-diary) or severe from the AE CRF.	Necrosis or exfoliative dermatitis

Table 5. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units from the e-diary) or mild from the AE CRF.	>5.0 cm to 10.0 cm (11 to 20 measuring device units from the e-diary) or moderate from the AE CRF.	>10 cm (>20 measuring device units from the e-diary) or severe from the AE CRF.	Necrosis
Pain (at the injection site)	Does not interfere with activity (mild from the e-diary or the AE CRF).	Interferes with activity (moderate from the e-diary or the AE CRF).	Prevents daily activity (severe from the e-diary or the 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).

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 (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, if the answer is not "no" for at least 1 day.

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

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

= Missing, if values are missing for all days (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 the vaccine group receiving sequential administration of qIRV/RSVpreF, the maximum severity will be derived as the highest severity grade across Vaccination 1 and Vaccination 2.

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's 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.

As there is a second vaccination at Visit A102, the date the reaction ended for Vaccination 1 should not be after the beginning of Vaccination 2. Therefore, if a reaction is ongoing at the time of Vaccination 2, the end date for the reaction after Vaccination 1 would be the date of the day before Vaccination 2, which will be used for the duration computation.

For the vaccine group receiving sequential administration of qIRV/RSVpreF, the duration will be calculated as total days after Vaccination 1 and Vaccination 2.

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.

For the vaccine group receiving sequential administration of qIRV/RSVpreF, the onset day will be calculated as the earliest day of onset after Vaccination 1 and after Vaccination 2.

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

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

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

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

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

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

For the vaccine group receiving sequential administration of qIRV/RSVpreF, if a local reaction is present on Day x either after Vaccination 1 or after Vaccination 2 for the same participant, that local reaction is considered as present on that day.

3.1.3.2. Systemic Events

Systemic events, including fever, fatigue, headache, vomiting, nausea, diarrhea, chills, new or worsened muscle pain, and new or worsened joint pain, are reported from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination with combination RSVpreF + qIRV, qIRV, RSVpreF, or placebo. The derivations for the systemic events, for each of the 5 vaccine groups as described below, will be handled similarly to the way local reactions are handled for the presence for each participant, severity level, duration, onset day, and systemic event on each and any day:

1. Presence (yes or no) of <u>each</u> systemic event on any day (Day 1 through Day 7) after vaccination.
2. Presence (yes or no) of <u>any</u> systemic event on any day (Day 1 through Day 7) after vaccination.
3. Maximum severity of <u>each</u> systemic event on any day (Day 1 through Day 7) after vaccination.
4. Maximum severity of <u>any</u> 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 <u>each</u> systemic event on each and any of the 7 days after Vaccination.
8. Presence (yes or no) of <u>any</u> systemic event on each and any of the 7 days after Vaccination.

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 the 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 to 38.4°C from the e-diary or mild grade from the AE CRF).
- Moderate (>38.4 to 38.9°C from the e-diary or moderate grade from the AE CRF).
- Severe (>38.9 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 in 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

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

For any AE reported in the CRF that was considered as reactogenicity (Section 3.1.3) during the clinical review and data-pooling process, this AE record will not be included in any of the derivations included in Section 3.1.3.3 and Section 3.1.3.4. However, if those reactogenicity AEs lead to discontinuation or were serious AEs, they will still be included in AE data.

The following derivations will be included for each participant:

1. Any AE reported within 1 month after vaccination: If the AE started on the same day of vaccination, and the AE start time is before the vaccination time, then this AE will not be counted. Otherwise, if the AE start time is missing or after the vaccination time, the AE will be included.
2. Any related AE reported within 1 month after vaccination: This is similar to the above except only the related AE is included (but excluding the related reactogenicity reported within 7 days of vaccination [Section 3.1.3]).
3. Any immediate AE reported after vaccination (AE start time is within 30 minutes after vaccination): Only those AEs that start on the same day of vaccination, and with nonmissing AE start time that is within 30 minutes of vaccination, will be included.
4. Any severe AE reported within 1 month after vaccination.

5. Any life-threatening AE reported within 1 month after vaccination.
6. Any AE leading to study withdrawal within 1 month after vaccination.
7. Any SAE reported within 1 month after vaccination.
8. Any AESI within 1 month after vaccination, based on the AE PT.

   The following events are considered AESIs:

   - Confirmed diagnosis of influenza.
   - Confirmed diagnosis of RSV infection.
   - Confirmed diagnosis of myocarditis or pericarditis within 4 weeks after Vaccination 1. See Section 3.6.3 for the evaluation of potential myocarditis or pericarditis.

Each of the above will be derived for the data presentation with 5 vaccine groups. Specifically, for the vaccine group receiving sequential administration of qIRV/RSVpreF, the endpoints will be derived after Vaccination 1 and Vaccination 2.

3.1.3.4. Serious Adverse Events

SAEs are collected throughout the study. The following variable will be derived:

- SAEs from Vaccination 1 throughout the study (for the 2 study groups).

3.2. SSB Primary Endpoint(s)

3.2.1. SSB Primary Safety Endpoints

The primary safety endpoints for Substudy B are the same as the primary safety endpoints for Substudy A (refer to Section 3.1.3), but the vaccine groups will be different.

The table below lists safety endpoints for Substudy B that will be derived and the more detailed derivations with the age groups of 50-64 years, 65+ years, and 50+ years will be applied.

Safety Endpoints	Vaccine Group (as Received)	
	(RSVpreF + qIRV) 1.0-mL	(RSVpreF + qIRV) 0.5-mL
Local reactions within 7 days after vaccination	Local reactions reported within 7 days after vaccination with the combination (RSVpreF + qIRV) 1.0-mL at Visit B101.	Local reactions reported within 7 days after vaccination with the combination (RSVpreF + qIRV) 0.5-mL at Visit B101.
Systemic events within 7 days after vaccination	Systemic events reported within 7 days after vaccination with the combination (RSVpreF + qIRV) 1.0-mL at Visit B101.	Systemic events reported within 7 days after vaccination with the combination (RSVpreF + qIRV) 0.5-mL at Visit B101.

Safety Endpoints	Vaccine Group (as Received)	
	(RSVpreF + qIRV) 1.0-mL	(RSVpreF + qIRV) 0.5-mL
AEs throughout the study	AEs reported from vaccination throughout the study among participants who received the combination (RSVpreF + qIRV) 1.0-mL at Visit B101.	AEs reported from vaccination throughout the study among participants who received the combination (RSVpreF + qIRV) o\0.5-mL at Visit B101.
SAEs throughout the study	SAEs reported from vaccination throughout the study among participants who received the combination (RSVpreF + qIRV) 1.0-mL at Visit B101.	SAEs reported from vaccination throughout the study among participants who received the combination (RSVpreF + qIRV) 0.5-mL at Visit B101.

The local reactions and systemic events in Substudy B will be the same as defined in Substudy A (Section 3.1.3.1 and Section 3.1.3.2) from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination, with combination (RSVpreF + qIRV) 1.0-mL or combination (RSVpreF + qIRV) 0.5-mL. The vaccine groups are different from Substudy A and the derivations described in the above table.

3.2.1.1. Adverse Events

In Substudy B, AEs will be collected throughout the study. The following derivations will be included for each participant:

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

2. Any related AE reported from vaccination throughout the study: This is similar to the above except only the related AE is included (but excluding the related reactogenicity reported within 7 days of vaccination [Section 3.1.3]).

3. Any immediate AE reported after vaccination (AE start time is within 30 minutes after vaccination): Only those AEs that start on the same day of vaccination, and with nonmissing AE start time that is within 30 minutes of vaccination, will be included.

4. Any severe AE reported from vaccination throughout the study.

5. Any life-threatening AE from vaccination reported throughout the study.

6. Any AE leading to study withdrawal after vaccination.

7. Any SAE reported from vaccination throughout the study.

8. Any AESI from vaccination throughout the study, based on the AE PT.

The following events are considered AESIs:

- Confirmed diagnosis of influenza.
- Confirmed diagnosis of RSV infection.
- Confirmed diagnosis of myocarditis or pericarditis within 4 weeks after vaccination. See Section 3.6.3 for the evaluation of potential myocarditis or pericarditis.

Each of the above will be derived for the data presentation with 2 vaccine groups and the age groups of 50-64 years, 65+ years and 50+ years.

The same algorithm as stated in Section 3.1.3, for any AE reported in the CRF that was considered as reactogenicity during the clinical review and data-pooling process, this AE record will not be included in any of the derivations included in Section 3.1.3.3 and Section 3.1.3.4. However, if those reactogenicity AEs lead to discontinuation or were serious AEs, they will still be included in AE data.

3.3. SSB Secondary Endpoint(s)

3.3.1. SSB Secondary RSV Immunogenicity Endpoints

RSV A– and RSV B–neutralizing antibody titers will be determined on sera collected at all 2 visits. The RSV NTs measured at the Month 1 visit after vaccination in both combination groups are relevant to the secondary RSV immunogenicity endpoints.

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

3.3.2. SSB Secondary HAI Immunogenicity Endpoints

HAI titers to the influenza strains will be determined on sera collected at all 2 visits. The immunogenicity results for HAI measured at the Month 1 visit after vaccination in both combination groups are relevant to the secondary HAI immunogenicity endpoints.

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

3.4. SSA and SSB Other Endpoint(s)

3.4.1. SSA and SSB Use of Antipyretic Medication Within 7 Days After Vaccination

The derivation for the use of antipyretic medication would be the same for both Substudy A and Substudy B.

The use of antipyretic medication within 7 days after vaccination is collected via the e-diary. The derivation will be similar to local reactions and systemic events, except there is no severity grading and the only data source will be from the e-diary.

3.4.2. SSA and SSB Exploratory Endpoints

In addition to the endpoints included in Section 3.1.1, Section 3.1.2, and Section 3.1.3, the following variables will be derived for exploratory endpoints for each participant.

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

RSV A– and RSV B–neutralizing antibody titers will be determined using the same method for both Substudy A and Substudy B at all eligible visits.

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 blood draw visit after vaccination. The numerator is the postvaccination value and the denominator is the prevaccination value. The RSV A/B NT fold rise is derived as the geometric mean of the RSV A NT fold rise and the RSV B NT fold rise.

For Substudy A: For combination RSVpreF + qIRV, assay results at Visit A101 will be used as before vaccination. For the sequential-administration group, assay results at Visit A102 will be used if both Visit A101 and Visit A102 data are available; otherwise, the assay results at Visit 1 will be used if only Visit 1 assay results are available.

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

3.4.2.2. HAI Titers

For both SSA and SSB: HAI titers to the influenza strains in combination RSVpreF + qIRV or qIRV alone will be determined on sera collected at the 1st visit and the 2nd visit.

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

3.4.2.3. HAI Seroprotection

For both SSA and SSB: HAI seroprotection is defined as an HAI titer ≥1:40. This will be derived for each participant for each strain at the 1st visit and 2nd visit.

3.4.2.4. HAI Seroconversion

For both SSA and SSB: HAI seroconversion from before the 1st visit to 1 month after qIRV administration (2nd visit) will be defined for each participant for each strain as follows.

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

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

3.5. Baseline Variables

Substudy A and Substudy B use the same derivation for the following baseline variables.

3.5.1. Baseline Definition

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

3.5.2. Demographics, Baseline Vital Signs, 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 86th birthday, the participant is 85 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.

Baseline blood pressure and pulse rate will be collected.

Participants' receipt of the most recent licensed influenza vaccination for the 2022-2023 northern hemisphere season, or the 2022 southern hemisphere season relative to study intervention, will be categorized as >120 days before study intervention administration and <=120 days before study intervention administration for SSA.

For SSB, the criteria will be changed to >180 days before study intervention administration and <=180 days before study intervention administration for latency categorization.

3.5.3. E-Diary Completion

An e-diary will be considered transmitted if any data for the local reactions and systemic events are present for any day. If all data are missing for all items (local reactions and systemic events) 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 at both Day 1 and Day 2.
- e-diary data transmitted from Day 1 to Day 3.
- e-diary data transmitted from Day 1 to Day 4.
- e-diary data transmitted from Day 1 to Day 5.
- e-diary data transmitted from Day 1 to Day 6.
- e-diary data transmitted for all 7 days.

3.5.4. 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.

Refer to Section 3.5.2 for latency categorization in licensed influenza vaccine receipt.

3.6. Safety Endpoints

3.6.1. Adverse Events

Guillain-Barre syndrome (from Day 1 through Day 43 after vaccination with RSVpreF or (RSVpreF+qIRV), where Day 1 is the day of vaccination), atrial fibrillation (from vaccination with RSVpreF or (RSVpreF+qIRV) through the Month 1 visit), and polyneuropathy (from Day 1 through Day 43 after vaccination with RSVpreF or (RSVpreF+qIRV), where Day 1 is the day of vaccination) have been identified as Tier 1 events for RSVpreF. The RSV program list of Tier 1 MedDRA PTs, maintained by the safety risk lead, is in the CAETeLiSt and is referenced in the safety surveillance review plan for the program. The current list of Tier 1 events should be confirmed to ensure that appropriate Tier 1 events will be used to produce final tables/graphs before conducting an analysis. Because RSVpreF is a vaccine component of the combination vaccine and is also study vaccine, these Tier 1 events are defined in this study.

3.6.2. Vital Sign Data

For both Substudy A and Substudy B, the temperature collected at baseline will only be used to assess any potential protocol deviation for a vaccination temporary delay. Therefore, it will not be included as a baseline variable. Only blood pressure and pulse rate will be included as a baseline vital-sign variable.

3.6.3. Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after Vaccination 1 must be specifically evaluated for possible myocarditis or pericarditis. ECG and measurement of troponin will be performed locally for potential myocarditis/pericarditis evaluation. These events will also be entered as AEs, which will link with signs and symptoms of potential cardiac disease by AE ID in the CRF. The AE verbatim term will be entered/modified in the CRF based on reviews/evaluations of various tests, according to the CRF completion guideline.

The variables in the table below will be derived for these assessments, and the derivation will be based on the AE verbatim term according to Tejtel[1]:

Brighton Collaboration case definition and level of diagnostic certainty	Protocol	Derivation
Level 1 definitive myocarditis	Confirmed myocarditis	AE verbatim=confirmed myocarditis
Level 1 definitive pericarditis	Confirmed pericarditis	AE verbatim=confirmed pericarditis
Level 2 probable myocarditis	Suspected or probable myocarditis	AE verbatim=suspected or Probable myocarditis
Level 2 probable pericarditis	Suspected or probable pericarditis	AE verbatim=suspected or Probable pericarditis
Level 3 possible myocarditis	Possible myocarditis	AE verbatim=possible myocarditis
Level 3 possible pericarditis	Possible pericarditis	AE verbatim=possible pericarditis

Brighton Collaboration case definition and level of diagnostic certainty	Protocol	Derivation
N/A	Potential myocarditis or pericarditis only	AE verbatim not in any of above 6 but with a nonmissing signs and symptoms page with symptom onset within 28 days after Vaccination 1

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.

Substudy A:

Participant Analysis Set	Description
Enrolled	All participants who have a signed ICD.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive the study intervention either in combination RSVpreF + qIRV, or as placebo, qIRV, or RSVpreF alone.
E-diary safety population	All enrolled participants who receive the study intervention either in combination RSVpreF + qIRV, or as placebo, qIRV, or RSVpreF alone, and having at least 1 day of e-diary data transferred.

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

Substudy A:

Defined Analysis Set	Description
Evaluable RSV immunogenicity population	All participants who meet the following criteria: • Are eligible for the study. • Receive the study intervention(s) to which they were randomized (RSVpreF + qIRV at Visit A101 for the combination group, and RSVpreF at Visit A102 for the sequential-administration group). • Have the 1-month postvaccination blood collection within 27 to 42 days after vaccination (Visits A102 to A101 for the combination group and Visits A103 to A102 for the sequential-administration group). • Have at least 1 valid and determinate RSV NT result at the 1-month postvaccination blood collection.

Defined Analysis Set	Description
	• Have no major protocol violations from randomization through the 1-month postvaccination blood collection.
Evaluable HAI immunogenicity population	All participants who meet the following criteria: • Are eligible for the study. • Receive the study intervention(s) to which they were randomized at Visit A101 (RSVpreF + qIRV in the combination group versus qIRV in the sequential-administration group). • Have the 1-month postvaccination blood collection for HAI assay within 27 to 42 days after vaccination (Visits A102 to A101). • Have at least 1 valid and determinate HAI result at the 1-month postvaccination blood collection. • Have no major protocol violations from randomization through the 1-month postvaccination blood collection (through Visit A102).
mITT immunogenicity population	All participants who were randomized and had at least 1 valid and determinate assay result at any time point after receiving study intervention (combination RSVpreF + qIRV, placebo, qIRV alone, or RSVpreF alone).

Like SSA, SSB analysis sets are descripted as following:

Substudy B:

Participant Analysis Set	Description
Enrolled	All participants who have a signed ICD.
Randomized population	All enrolled participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive the study intervention (0.5 mL or 1.0 mL).
E-diary safety population	All enrolled participants who receive the study intervention (0.5 mL or 1.0 mL) and with at least 1 day of e-diary data transferred.
Evaluable immunogenicity population	All participants who meet the following criteria: • Are eligible for the study. • Receive the study intervention to which they were randomized at Visit B101. • Have the 1-month postvaccination blood collection for serology assay testing within an appropriate window. • Have at least 1 valid and determinate assay result at the 1-month postvaccination blood collection. • Have no major protocol violations from randomization through the 1-month postvaccination blood collection (through Visit B102).
mITT immunogenicity population	All participants who are randomized and have at least 1 valid and determinate assay result after receiving study intervention.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis in Substudy A and Substudy B.

The estimands corresponding to each primary, secondary, or exploratory objective are described in Section 2.2.

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.[2] The 95% CI will be presented in terms of percentage.

2. The 95% CI for the difference in the proportions (between vaccine groups) will be computed using the Miettinen and Nurminen method.[3] 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 t distribution, and then exponentiating the results.

5.2.2.2. Geometric Mean Fold Rises

GMFRs will be calculated as the group mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. GMFRs are limited to participants with nonmissing values at both time points. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

The GMRs will be calculated as the mean of the difference of logarithmically 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 logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

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

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

5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the “any day (Day 1 through Day 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 3.1.3. 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).

Based on data from available studies, the missing data for reactogenicity are minimal, which is consistent with Li et al.[4] No sensitivity analysis is planned for reactogenicity data.

5.3.2. Immunogenicity Data

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

For calculating a fold rise, < LLOQ will be converted to 0.5 × LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only 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 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.[5]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

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

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.2.1.1).
- Analysis set: Evaluable RSV immunogenicity population (Section 4).
- Analysis methodology: GMR, defined as the ratio of RSV A– and RSV B–neutralizing GMTs in the combination RSVpreF + qIRV group at Visit A102 to that in the sequential-administration RSVpreF group at Visit A103, will be summarized along with the 95% CI (Section 5.2.2.3).
- Intercurrent events: Data collected after an intercurrent event will not be included (Section 2.2.1.1).
- Missing data: Missing data will not be imputed (Section 5.3.2).
- RSV A– and RSV B–neutralizing GMTs and sample size in the combination group at Visit A102, and that in the sequential-administration RSVpreF group at Visit A103, will be presented.
- GMRs and 95% CIs for the GMRs, using the Student t distribution, will be presented (Section 5.2.2.3).
- Forest plots with GMRs and the 95% CIs will be presented.

6.1.1.2. Supplementary Analysis

To support the assessment of immunogenicity, estimands as specified in Section 2.2.4, using the treatment policy strategy, will be summarized with the mITT immunogenicity population using the same presentation (except the forest plots) as specified in the main analysis.

6.1.2. HAI Titers for Substudy A

6.1.2.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.2.1.2).
- Analysis set: Evaluable HAI immunogenicity population (Section 4).
- Analysis methodology: GMR, defined as the ratio of HAI GMTs in the combination RSVpreF + qIRV group to that in the sequential-administration qIRV group for each strain at Visit A102, will be summarized along with the 95% CI (Section 5.2.2.3).
- Intercurrent events: Data collected after an intercurrent event will not be included (Section 2.2.1.2).
- Missing data: Missing data will not be imputed (Section 5.3.2).
- HAI GMTs and sample size in the combination RSVpreF + qIRV group, and that in the sequential-administration qIRV group at Visit A102, will be presented.
- GMR and 95% CI for the GMR, using the Student t distribution, will be presented (Section 5.2.2.3).
- Forest plots with GMRs and the 95% CIs will be presented.

6.1.2.2. Supplementary Analyses

To support the assessment of immunogenicity, estimands as specified in Section 2.2.4, using the treatment policy strategy, will be summarized with the mITT immunogenicity population using the same presentation (except the forest plots) as specified in the main analysis.

6.1.3. Local Reactions and Systemic Events for Substudy A

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

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.3.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CIs of the proportion of participants reporting each event will use the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: All data collected are included; partially missing diary data are imputed as "no" (Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented for each vaccine group for each vaccination.
- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event throughout the 7 days will be plotted for each vaccine group for each vaccination. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.3.2. Supplementary Analysis

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

- Duration (days) of each local reaction and each systemic event after vaccination.
- Onset day of each local reaction and each systemic event after vaccination.
- Presence of any local reaction and any systemic event on each of the 7 days, for the first 2 days (with nonmissing reactogenicity data from Day 1 through Day 2), first 3 days, first 4 days, first 5 days, first 6 days, all 7 days (nonmissing reactogenicity data for all 7 days), and for "any day (Day 1 through Day 7)."

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

6.1.4. AEs for Substudy A

Participants will be summarized by vaccine group as defined in Section 3.1.3.3. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.4.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.3.2).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CIs of the proportion of participants reporting those events will use the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: All data collected are included.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented for each vaccine group for each analysis interval (Section 5.2.1).
- Bar charts with the proportions of participants for each variable within the specified interval will be plotted for each vaccine group for each analysis interval. The bars may be divided into relatedness categories to highlight the proportions of participants with related events.

6.1.4.2. Supplementary Analysis

To support the assessment of AEs, the following endpoints, 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 vaccination.
- Related AEs reported within 1 month after vaccination.
- Severe AEs reported within 1 month after vaccination.
- Life-threatening AEs reported within 1 month after vaccination.
- AEs leading to withdrawal reported within 1 month after vaccination.
- AESIs reported within 1 month after vaccination.
- SAEs reported within 1 month after vaccination.

6.1.5. SAEs for Substudy A

SAEs reported throughout the study will be summarized with the safety population using the same presentation as specified in Section 6.1.4.1.

6.1.6. Substudy B

The primary endpoints for Substudy B are the main safety endpoints, similar to Substudy A in Section 6.1.3, Section 6.1.4, and Section 6.1.5. The reactogenicity, AE, and SAE endpoints as described in Section 3.2.1 will be summarized with the safety population using the same presentation, as specified in Section 6.1.3, Section 6.1.4, and Section 6.1.5, respectively

6.2. Secondary Endpoint

No secondary endpoint is defined in the Substudy A.

6.2.1. Secondary Endpoints for RSV A– and RSV B–Neutralizing Antibody Titers for Substudy B

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.2.1.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis methodology: GMR, defined as the ratio of RSV A– and RSV B–neutralizing GMTs in the 2 combination (RSVpreF + qIRV) 1.0-mL and 0.5-mL groups at Visit B102 will be summarized along with the 95% CI (Section 5.2.2.3).
- Intercurrent events: Data collected after an intercurrent event will not be included (Section 2.2.1.1).
- Missing data: Missing data will not be imputed (Section 5.3.2).
- RSV A– and RSV B–neutralizing GMTs and sample size in the 2 combination groups at Visit B102 will be presented overall and by age group.
- GMRs and 95% CIs for the GMRs, using the Student t distribution, will be presented (Section 5.2.2.3) overall and by age group.

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, will be summarized with the mITT immunogenicity population using the same presentation as specified in the main analysis.

6.2.2. Secondary Endpoints for HAI Titers for Substudy B

6.2.2.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.2.1.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis methodology: GMR, defined as the ratio of HAI GMTs in the 2 combination (RSVpreF + qIRV) 1.0-mL and 0.5-mL groups at Visit B102 will be summarized along with the 95% CI (Section 5.2.2.3).
- Intercurrent events: Data collected after an intercurrent event will not be included (Section 2.2.1.2).
- Missing data: Missing data will not be imputed (Section 5.3.2).
- HAI GMTs and the sample size in the 2 combination groups at Visit B102 will be presented for each age group and overall.
- GMRs and 95% CI for the GMRs, using the Student t distribution, will be presented (Section 5.2.2.3) overall and by age group.

6.2.2.2. Supplementary Analyses

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

6.2.3. Other Endpoint(s)

The analysis in this section will be the same for Substudy A and substudy B.

6.2.3.1. Use of Antipyretic Medication Within 7 Days After Vaccination

The use of antipyretic medication within 7 days after vaccination will be summarized along with systemic events, except there is no severity grading. Onset and duration will also be summarized. Although it is included in the systemic events, use of antipyretic medication will not be considered as "any systemic event."

6.2.3.2. Immunogenicity as Measured by NTs and HAIs

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

GMTs of NTs for each RSV subgroup (A or B) and RSV A/B combined, and GMTs of influenza strain-specific HAI titers at each applicable time point, will be descriptively summarized with 2-sided 95% CIs for each vaccine group.

GMFRs of NTs for each RSV subgroup (A or B) and RSV A/B combined, from before vaccination to each applicable postvaccination time point, and GMFRs of influenza strain-specific HAI titers from before vaccination to 1 month postvaccination, will be descriptively summarized with 2-sided 95% CIs for each vaccine group.

RCDC for each RSV subgroup (A or B) NTs at 1 month after RSVpreF (or combination) vaccination and RCDC for influenza strain-specific HAI titer at 1 month after qIRV (or combination) vaccination will be plotted for each group.

Analysis will be performed in the evaluable RSV immunogenicity population and evaluable HAI immunogenicity population.

6.2.4. HAI Seroprotection and Seroconversion

Descriptive statistics, including the proportion (%) of participants with seroprotection, seroconversion and 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 strain in each vaccine group at both Visit A101 and Visit A102 for seroprotection, and at Visit A102 for seroconversion, in the evaluable HAI immunogenicity population for SSA. Similarly, the summary will be provided at both Visit B101 and Visit B102 for seroprotection and at Visit B102 for seroconversion, in the evaluable immunogenicity population for SSB.

6.3. Subset Analyses

Substudy A: CCI [redacted]

Substudy B: CCI [redacted]

6.4. Baseline and Other Summaries and Analyses

The analyses in this section will be the same for Substudy A and Substudy B.

6.4.1. Baseline Summaries

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

Summary data will also be presented for the evaluable immunogenicity population(s).

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

Baseline blood pressure and pulse rate will be presented.

6.4.2. Study Conduct and Participant Disposition

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

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

Participants with important protocol deviations from vaccination through the end of the study will be summarized among the safety population.

The e-diary completion rate will be summarized for the safety population, by vaccine group (in Section 3.1.3 for Substudy A and in Section 3.2.1 for Substudy B), as well as summarized with the categorized days specified in Section 3.5.3.

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

6.4.3. Nonstudy Vaccines

Nonstudy vaccines recorded after signing the informed consent through the end of the study will be categorized according to the WHODrug Dictionary, and may be summarized by vaccine group and for all participants included in the safety population.

A listing may be used to replace the table.

6.5. Safety Summaries and Analyses

6.5.1. Adverse Events

For both SSA and SSB: For all of the AEs categorized in Section 3.1.3.3 and Section 3.1.3.4, each individual AE including SAE after vaccination will be categorized by the MedDRA PT and descriptively summarized with count, percentage, and 95% CI for vaccine group.

For Tier 1 events, the 2-sided 95% CIs for the difference in the percentage of participants reporting the events between the RSVpreF contained group and the control group will be calculated using the test statistic proposed by Miettinen and Nurminen[3]; in addition, the asymptotic p-values will also be presented for the difference 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.

Because all participants enrolled in this study are expected to receive either RSVpreF or (RSVpreF+qIRV), there is no control in this study. Therefore, the intervention group will be all participants who received (RSVpreF+qIRV) or RSVpreF from both SSA and SSB, and the control group will be from RSVpreF pivotal Phase 3 study (C3671013) who received placebo only. The count for each Tier 1 event and denominator from C3671013 placebo group will be provided in this Tier 1 AE analysis.

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 selecting 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.

6.5.2. Myocarditis or Pericarditis

The variable derived in Section 3.5.3 will be summarized with count, percentage, and 95% CI by vaccine group only at Visit 1 for either Substudy A or Substudy B.

A listing for ECG and measurement of troponin for potential myocarditis/pericarditis evaluation will be provided. Symptoms, ECG results, troponin level, cardiac study results, cardiac function evaluation, and final diagnosis results will all be listed for any participants with signs and symptoms onset within 28 days after Vaccination 1.

7. INTERIM ANALYSES

No interim analysis is planned for either Substudy A or Substudy B.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1 Tejtel S, Munoz F, Al-Ammouri I, et al. Myocarditis and pericarditis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 40. 2022;1499-1511.

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

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

4 Li X, Wang WWB, Liu GF, et al. Handling missing data in vaccine clinical trials for immunogenicity and safety evaluation. J Biopharm Stat. 2011;21(2):294-310.

5 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
app	application
BLQ	below the limit of quantitation
CAETeLiSt	custom adverse event term list system
CBER	Center for Biologics Evaluation and Research (United States)
CI	confidence interval
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
FDA	Food and Drug Administration (United States)
GBS	Guillain-Barre syndrome
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition
ICD	informed consent document
ID	identification
IRT	interactive response technology
LLOQ	lower limit of quantitation
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NT	neutralizing titer
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
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
WHO	World Health Organization

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