Protocol C5481001 – Substudy A

A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED VACCINE CANDIDATE(S) AGAINST INFECTIOUS RESPIRATORY ILLNESSES, INCLUDING COVID-19 AND RSV, IN HEALTHY INDIVIDUALS – SUBSTUDY A

Statistical Analysis Plan (SAP)

Version: 3

Date: 01 August 2023

TABLE OF CONTENTS

LIST OF TABLES 5
APPENDICES 5
1. VERSION HISTORY 6
2. INTRODUCTION 7
2.1. Modifications to the Analysis Plan Described in the Protocol 7
2.2. Study Objectives, Endpoints, and Estimands 8
2.2.1. Primary Estimands 10
2.2.1.1. Primary Immunogenicity Estimands for Combination Vaccine Coadministration With QIV Noninferiority Objective 10
2.2.1.2. Primary Immunogenicity Estimands for Combination Vaccine Noninferiority Objective 11
2.2.1.3. Primary Safety Estimands 13
2.2.2. Secondary Estimands 14
2.2.2.1. Secondary Immunogenicity Estimands for 3-Vaccine Coadministration Noninferiority Objective 14
2.2.2.2. Secondary Immunogenicity Estimands for RSVpreF and BNT162b2 Coadministration Noninferiority Objective 14
2.2.3. Additional Estimands 14
2.3. Study Design 15
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 17
3.1. Primary Endpoints 17
3.1.1. Primary Immunogenicity Endpoints 17
3.1.2. Primary Safety Endpoints 17
3.1.2.1. Local Reactions Within 7 Days After Vaccination 18
3.1.2.2. Systemic Events Within 7 Days After Vaccination 20
3.1.2.3. Adverse Events and Serious Adverse Events 21
3.2. Secondary Endpoints 23
3.3. Other Endpoints 23
3.3.1. Immunogenicity Results Fold Rise 23
3.3.2. RSV A/B 23

3.3.3. HAI Seroprotection 23
3.3.4. HAI Seroconversion 23
3.3.5. SARS-CoV-2 Seroresponse 23
3.3.6. RSV Seroresponse 24
3.4. Baseline Variables 24
3.4.1. Baseline Definition 24
3.4.2. Demographics, Baseline, and Medical History 24
3.4.3. E-Diary Completion 24
3.4.4. Nonstudy Vaccines 25
3.5. Safety Endpoints 25
3.5.1. Adverse Events 25
3.5.2. Vital Sign Data 26
3.5.3. Myocarditis or Pericarditis 26
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 26
5. GENERAL METHODOLOGY AND CONVENTIONS 27
5.1. Hypotheses and Decision Rules 27
5.1.1. Statistical Hypotheses for Combined Vaccine Coadministered With QIV 27
5.1.2. Statistical Hypotheses for Combined Vaccine Alone 28
5.1.3. Statistical Hypotheses for Coadministration of 3 Individual Vaccines 28
5.1.4. Statistical Hypotheses for Coadministration of 2 Individual Vaccines 29
5.1.5. Multiplicity Adjustment 29
5.2. General Methods 29
5.2.1. Analyses for Binary Data 30
5.2.2. Analyses for Continuous Data 30
5.2.2.1. Geometric Means 30
5.2.2.2. Geometric Mean Fold Rises 30
5.2.2.3. Geometric Mean Ratios 30
5.2.2.4. Reverse Cumulative Distribution Curves 31
5.2.2.5. Analysis of Covariance 31
5.3. Methods to Manage Missing Data 31
5.3.1. Safety Data 31

5.3.1.1. Reactogenicity Data 31
5.3.2. Immunogenicity Data 32
6. ANALYSES AND SUMMARIES 32
6.1. Primary Endpoints 32
6.1.1. Primary Immunogenicity Endpoints for Combined Vaccine Coadministered With QIV (Group 1) Noninferiority Objective 32
6.1.1.1. Main Analysis 32
6.1.1.2. Supplementary Analysis 33
6.1.2. Primary Immunogenicity Endpoints for Combined Vaccine (Group 2) Noninferiority Objective 33
6.1.2.1. Main Analysis 33
6.1.2.2. Supplementary Analysis 33
6.1.3. Local Reactions and Systemic Events 33
6.1.3.1. Main Analysis 34
6.1.3.2. Supplementary Analysis 34
6.1.3.3. Sensitivity Analysis 34
6.1.4. AEs and SAEs 35
6.1.4.1. Main Analysis 35
6.1.4.2. Supplementary Analysis 35
6.1.4.3. Sensitivity Analysis 36
6.2. Secondary Endpoints 36
6.3. Other Endpoints 36
6.3.1. GMTs and GMFRs 36
6.3.2. HAI Seroprotection and HAI Seroconversion 36
6.3.3. SARS-CoV-2 NT Seroresponse 36
6.3.4. RSV NT Seroresponse 37
6.3.5. Additional Analysis 37
6.3.5.1. Descriptive Between-Group Comparisons 37
6.3.5.2. Sensitivity Analysis 37
6.3.5.3. Combined Group 1 and Group 2 Analysis 38
6.4. Subset Analyses 38
6.5. Baseline and Other Summaries and Analyses 38

6.5.1. Study Conduct and Participant Disposition 38
6.6. Safety Summaries and Analyses 39
6.6.1. Adverse Events 39
6.6.2. Myocarditis or Pericarditis 39
7. INTERIM ANALYSES 39
7.1. Introduction 39
7.1.1. Analysis Timing 39
7.1.2. Blinding and Unblinding 40
8. REFERENCES 40
9. APPENDICES 41

LIST OF TABLES

Table 1. Summary of Changes 6
Table 2. Derived Variables for Each Local Reaction 18
Table 3. Derived Variables for Any Local Reaction 19
Table 4. Grading Scale for Local Reactions 19

APPENDICES

Appendix 1. List of Abbreviations 41

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 02 May 2023	Original 22 Apr 2023	N/A	N/A
2 23 June 2023	Original 22 Apr 2023	1. Included Guillain-Barre syndrome, atrial fibrillation, and polyneuropathy as Tier 1 events for RSVpreF per CBER request; provided additional information on Tier 2 and Tier 3 events. 2. Clarified the AESI analysis is for the protocol-specified AESIs. 3. Typo correction.	1. Added the rationale and/or definition of Tier 1, Tier 2 and Tier 3 events in Section 3.5.1; added the analysis of Tier 1 events and the description of the 3-tier approach in Section 6.6.1. 2. Added "protocol-specified" to AESIs in Section 3.1.2.3. 3. Deleted "(the combination group and the sequential-administration group)" in Section 5.2.2.3.
3 01 August 2023	Original 22 Apr 2023	1. Updated reactogenicity analysis based on CBER feedback for other vaccine program studies.	1. Updated to include both related and unrelated AEs within 7 days after vaccination for pooling with reactogenicity data in Section 3.1.2. Added e-diary completion to Section 3.4.3 and the details in Section 6.5.1. 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 and Section 6.1.4, clarified analysis of local reactions and systemic events and added sensitivity analyses for reactogenicity maximum severity and AE summary.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
		2. Updated immunogenicity analysis based on CBER feedback to RSV studies and the clinical development plan on combined vaccine.	2. Added seroresponse for RSV A and RSV B in Section 3.3.6 and its analysis in Section 6.3.4. Added a descriptive immunogenicity analysis for combining Groups 1 and 2 in Section 6.3.5.3.
		3. Clarified the derivation for cases of myocarditis or pericarditis.	3. Updated Section 3.5.3.
		4. Updated the meaning of "N-binding antibody" at baseline.	4. Updated Section 3.4.2.
		5. Typo correction.	5. Changed "GMR of NTs" to "GMR of HAI titers" in the secondary immunogenicity objective on QIV (Group 7 versus Group 5) in the Section 2.2 table, and changed "these assessment" to "these assessments" in Section 3.5.3.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C5481001 – Substudy A.

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	Estimands	Endpoints
Primary Safety	To describe the safety and tolerability of [RSVpreF+BNT162b2]	In participants receiving study intervention, the percentage of participants reporting: • Local reactions within 7 days following vaccination • Systemic events within 7 days following vaccination • AEs from vaccination through 1 month after vaccination • SAEs from vaccination through 6 months after vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity	To demonstrate that the immune responses elicited by [RSVpreF+BNT162b2] when coadministered with QIV are noninferior to those elicited by each vaccine alone: 1. RSVpreF alone (Group 1 vs Group 4) 2. Bivalent BNT162b2 alone (Group 1 vs Group 3) 3. QIV alone (Group 1 vs Group 5)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 1 and 4): • GMR of NTs at 1 month after vaccination in Group 1 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 1 to Group 4 for RSV subgroup B 2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 1 and 3): • GMR of NTs at 1 month after vaccination in Group 1 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 1 to Group 3 for SARS-CoV-2 reference strain 3. In participants in compliance with the key protocol criteria (evaluable participants for Groups 1 and 5): • GMR of HAI titers at 1 month after vaccination in Group 1 to Group 5 for each influenza strain included in QIV	1. RSV A and RSV B NTs 2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs 3. HAI titers for each strain contained in the QIV

Type	Objectives	Estimands	Endpoints
Primary Immunogenicity	To demonstrate that the immune responses elicited by [RSVpreF+BNT162b2] are noninferior to those elicited by each vaccine alone: 1. RSVpreF alone (Group 2 vs Group 4) 2. Bivalent BNT162b2 alone (Group 2 vs Group 3)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 2 and 4): • GMR of NTs at 1 month after vaccination in Group 2 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 2 to Group 4 for RSV subgroup B 2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 2 and 3): • GMR of NTs at 1 month after vaccination in Group 2 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 2 to Group 3 for SARS-CoV-2 reference strain	1. RSV A and RSV B NTs 2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs
Secondary Immunogenicity	To demonstrate that the immune responses elicited by RSVpreF, bivalent BNT162b2, and QIV, when administered concomitantly, are noninferior to those elicited by each vaccine alone: 1. RSVpreF (Group 7 vs Group 4) 2. Bivalent BNT162b2 (Group 7 vs Group 3) 3. QIV (Group 7 vs Group 5)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 7 and 4): • GMR of NTs at 1 month after vaccination in Group 7 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 7 to Group 4 for RSV subgroup B 2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 7 and 3): • GMR of NTs at 1 month after vaccination in Group 7 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 7 to Group 3 for SARS-CoV-2 reference strain 3. In participants in compliance with the key protocol criteria (evaluable participants for Groups 7 and 5): • GMR of HAI titers at 1 month after vaccination in Group 7 to Group 5 for each influenza strain included in the QIV	1. RSV A and RSV B NTs 2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs 3. HAI titers for each strain contained in the QIV

Type	Objectives	Estimands	Endpoints
Secondary Immunogenicity	To demonstrate that the immune responses elicited by RSVpreF and bivalent BNT162b2 when administered concomitantly are noninferior to those elicited by each vaccine alone: 1. RSVpreF (Group 6 vs Group 4) 2. Bivalent BNT162b2 (Group 6 vs Group 3)	1. In participants in compliance with the key protocol criteria (evaluable participants for Groups 6 and 4): • GMR of NTs at 1 month after vaccination in Group 6 to Group 4 for RSV subgroup A • GMR of NTs at 1 month after vaccination in Group 6 to Group 4 for RSV subgroup B 2. In participants in compliance with the key protocol criteria (evaluable participants for Groups 6 and 3): • GMR of NTs at 1 month after vaccination in Group 6 to Group 3 for SARS-CoV-2 Omicron BA.4/BA.5 • GMR of NTs at 1 month after vaccination in Group 6 to Group 3 for SARS-CoV-2 reference strain	1. RSV A and RSV B NTs 2. SARS-CoV-2 Omicron BA.4/BA.5 and reference-strain NTs
Exploratory	To further describe the immune responses elicited by [RSVpreF+BNT162b2]	• N/A	• N/A

2.2.1. Primary Estimands

2.2.1.1. Primary Immunogenicity Estimands for Combination Vaccine Coadministration With QIV Noninferiority Objective

The primary estimands for the first primary immunogenicity objective will use the hypothetical strategy to estimate the immune response difference elicited from Group 1, compared with Groups 3, 4, and 5, respectively. In other words, the immune response is estimated in the hypothetical setting where participants follow the vaccines administered and protocol requirements as directed. It includes the following 5 attributes:

- **Treatment condition**: Randomized to Group 1, 3, 4, or 5.
- **Population**: Participants as defined by the study inclusion/exclusion criteria for Substudy A.
- **Variables**: Each of the following serology results measured at Visit A102:
  - RSV subgroup A NT
  - RSV subgroup B NT
  - SARS-CoV-2 Omicron BA.4/BA.5 NT

- SARS-CoV-2 reference-strain NT
- Influenza A (H1N1) HAI titer
- Influenza A (H3N2) HAI titer
- Influenza B1 (Victoria) HAI titer
- Influenza B2 (Yamagata) HAI titer

- **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 (participants who were randomized to Group 1 should have received both [RSVpreF+BNT162b2] and QIV; participants who were randomized to Group 4 should have received RSVpreF; participants who were randomized to Group 3 should have received BNT162b2; and participants who were randomized to Group 5 should have received QIV).
  2. The participant did not meet the 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 from the vaccination and blood draw visit.
  4. Blood was taken outside the window of 27 to 42 days after vaccination for immunogenicity evaluation.

The clinical question of interest is based on whether immune response elicited by [RSVpreF+BNT162b2], when coadministered with QIV, without any influence from any other immune-modifying drugs or vaccines and measured within a homogeneous time window, is noninferior to that elicited by RSVpreF, BNT162b2, and QIV alone. 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**: GMR, defined as the ratio of each applicable variable GMT, between Group 1 and Groups 3, 4, and 5, respectively.

2.2.1.2. Primary Immunogenicity Estimands for Combination Vaccine Noninferiority Objective

The primary estimands for the second primary immunogenicity objective will use the hypothetical strategy to estimate the immune response difference elicited from Group 2, compared with Group 3 and Group 4, respectively. In other words, the immune response is estimated in the hypothetical setting where participants follow the vaccines administered and protocol requirements as directed. It includes the following 5 attributes:

- **Treatment condition**: Randomized to Group 2, 3, or 4.

- **Population**: Participants as defined by the study inclusion/exclusion criteria for Study C5481001 – Substudy A.
- **Variables**: Each of the following serology results measured at Visit A102:
  - RSV subgroup A NT
  - RSV subgroup B NT
  - SARS-CoV-2 Omicron BA.4/BA.5 NT
  - SARS-CoV-2 reference-strain NT
- **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 (participants who were randomized to Group 2 should have received [RSVpreF+BNT162b2]; participants who were randomized to Group 4 should have received RSVpreF; and participants who were randomized to Group 3 should have received BNT162b2).
  2. The participant did not meet the 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 from the vaccination and blood draw visit.
  4. Blood was taken outside the window of 27 to 42 days after vaccination for immunogenicity evaluation.

The clinical question of interest is based on whether immune response elicited from [RSVpreF+BNT162b2], without any influence from any other immune-modifying drugs or vaccines and measured within a homogeneous time window, is noninferior to that elicited from RSVpreF and BNT162b2 alone. 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**: GMR, defined as the ratio of each applicable variable GMT, between Group 2 and Groups 3 and 4, respectively.

2.2.1.3. Primary Safety Estimands

2.2.1.3.1. Reactogenicity Estimands

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

Reactogenicity estimands have the following 5 attributes:

- **Treatment condition**: [RSVpreF+BNT162b2] coadministered with QIV, [RSVpreF+BNT162b2], BNT162b2, RSVpreF, QIV, RSVpreF coadministered with BNT162b2, and RSVpreF coadministered with BNT162b2 and QIV.
- **Population**: Participants as defined by the study inclusion/exclusion criteria for Substudy A.
- **Variables**: Each item included in the e-diary reported from Days 1 through 7 after vaccination (refer to Section 3.1.2.1 and Section 3.1.2.2).
- **Intercurrent events**: All data collected after the intercurrent event will be included.
- **Population-level summary**: The rates of variables (each reported 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 3.1.2.3).
- **Population-level summary**: The rates of the variable (any AE reported within 1 month after vaccination) in each treatment condition.

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 6 months after vaccination (Section 3.1.2.3).

2.2.2. Secondary Estimands

2.2.2.1. Secondary Immunogenicity Estimands for 3-Vaccine Coadministration Noninferiority Objective

The estimand attributes are the same as the first primary immunogenicity estimand (Section 2.2.1.1), except:

- **Treatment condition**: Randomized to Group 7, 3, 4, or 5.
- **Intercurrent events:** Participants who were randomized to Group 7 should have received all 3 individual vaccines: RSVpreF, BNT162b2, and QIV.
- **Population-level summary**: GMR, defined as the ratio of each applicable variable GMT, between Group 7 and Groups 3, 4, and 5, respectively.

2.2.2.2. Secondary Immunogenicity Estimands for RSVpreF and BNT162b2 Coadministration Noninferiority Objective

The estimand attributes are the same as the second primary immunogenicity estimand (Section 2.2.1.2), except:

- **Treatment condition**: Randomized to Groups 6, 3, and 4.
- **Intercurrent events:** Participants who were randomized to Group 6 should have received both individual vaccines: RSVpreF and BNT162b2.

  Participants who were randomized to Group 6 should have received 2 individual vaccines: RSVpreF and BNT162b2.
- **Population-level summary**: GMR, defined as the ratio of each applicable variable GMT, between Group 6 and Groups 3 and 4, respectively.

2.2.3. Additional Estimands

Additional estimands, as supplementary analyses to support the primary and secondary immunogenicity objectives, are defined. The table below lists the variables and strategies for addressing intercurrent events, which are listed in Sections 2.2.1.1, 2.2.1.2, and 2.2.2 for the immunogenicity objectives. The remaining 4 estimand attributes (treatment condition, variables, population, and population-level summary) are the same for each objective.

Objective	Intercurrent Events Handling Strategy
Primary combination vaccine coadministration with QIV noninferiority	Treatment policy
Primary combination vaccine noninferiority	Treatment policy
Secondary 3-vaccine coadministration noninferiority	Treatment policy
Secondary RSVpreF and BNT162b2 coadministration noninferiority	Treatment policy

2.3. Study Design

This is a Phase 1/2 randomized, parallel-group, observer-blinded substudy to assess the safety, tolerability, and immunogenicity of a combined RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine, [RSVpreF+BNT162b2], administered concomitantly with a seasonal influenza vaccine or administered alone. Approximately 1050 healthy participants ≥65 years of age will be enrolled and randomized to 7 groups across 2 strata, as illustrated below.

All participants will be asked to complete a reactogenicity e-diary for 7 days following vaccination. AEs and SAEs will be collected from the signing of informed consent through Visit A102 (1-month follow-up visit). SAEs will be collected from the signing of informed consent through Visit A103 (6-month telephone contact).

Blood samples will be collected for immunogenicity assessments prior to vaccination at Visit A101 and 1 month after vaccination (Visit A102). Immunogenicity measured by HAI titers for the matched seasonal strains (2×A, 2×B) recommended by WHO will be assessed for Groups 1, 5, and 7; immunogenicity measured by SARS-CoV-2 neutralization assay (both reference strain and Omicron BA.4/BA.5) will be assessed for Groups 1, 2, 3, 6, and 7; and immunogenicity measured by RSV A and RSV B serum NTs will be assessed for Groups 1, 2, 4, 6, and 7.

	Vaccination			1-Month Follow-Up Visit	6-Month Telephone Contact
Approximate Month (Visit Window)	0 (Day 1)			1 (28 to 35 Days After Vaccination)	6 (175 to 189 Days After Vaccination)
Visit Identifier	Visit A101			Visit A102	Visit A103
	Vaccination 1 (Right Arm)	Vaccination 2 (Left Arm)	Vaccination 3 (Right Arm)		
Group 1 (n=150)	Combination [RSVpreF+BNT162b2]	QIV			
Group 2 (n=150)	Combination [RSVpreF+BNT162b2]	Placebo			
Group 3 (n=150)	Bivalent BNT162b2	Placebo			
Group 4 (n=150)	RSVpreF	Placebo			
Group 5 (n=150)	QIV	Placebo			
Group 6[a] (n=150)	Bivalent BNT162b2	Placebo	RSVpreF		
Group 7[a] (n=150)	Bivalent BNT162b2	QIV	RSVpreF		

Blood collection Telephone contact

a. Separate administration sites on right arm by 1 inch (2.5 cm).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

Immunogenicity measured by HAI titers for the matched seasonal strains (2×A, 2×B) recommended by WHO will be assessed for Groups 1, 5, and 7; immunogenicity measured by SARS-CoV-2 neutralization assay (both reference strain and Omicron BA.4/BA.5) will be assessed for Groups 1, 2, 3, 6, and 7; and immunogenicity measured by RSV A and RSV B serum NTs will be assessed for Groups 1, 2, 4, 6, and 7. An unblinded statistician will send the barcode listings to sample management for specific assay testing.

Only the immunogenicity results measured at the Month 1 visit from each applicable group are relevant to the primary endpoint.

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

3.1.2. Primary Safety Endpoints

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

Based on feedback from 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 does 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 a start time are defaulted to AEs reported after vaccination. Following these review steps, those AEs reported within 7 days after vaccination that match flagged PTs will be considered as reactogenicity data. If the same reactogenicity event 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 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. 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 will not be used for derivation, because doing so may inflate the denominator and bias the analysis, since participants who did not transfer e-diary data may be less likely to report reactogenicity data. 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.

3.1.2.1. 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. Any reported reactogenicity events in the AE CRF during the e-diary collection period are included in the derivation discussed below.

This section describes derivations with details for the assessment of local reactions: presence, maximum severity, duration, and onset day of local reactions.

3.1.2.1.1. Presence of Local Reactions Within 7 Days After Vaccination

For the summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after vaccination, the following variables will be derived for each participant included:

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

   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) after vaccination	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) after vaccination.

   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) after vaccination	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.

3.1.2.1.2. 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 assessments 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 analysis:

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

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

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

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

= *Highest grade* (maximum severity) within 7 days after vaccination (either from the e-diary or in the AE CRF), 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) after vaccination.

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

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

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

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

3.1.2.1.3. Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as 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.

3.1.2.1.4. Onset Day of Each Local Reaction

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

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

3.1.2.2. Systemic Events Within 7 Days After Vaccination

Systemic events, including fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, 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 any study intervention. 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 severe systemic event on each and any day.

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

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. Any measure with degrees Fahrenheit will be converted to degrees Celsius for analysis. 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, and documented >40.0°C via CRF query or other sources).

Any temperature that is confirmed as incorrect will use the correct temperature for analysis and those for which the correct temperature is unknown will not be included in the analysis.

3.1.2.3. Adverse Events and Serious Adverse Events

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

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

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

2. Any related AE reported through 1 month after vaccination: This is similar to the above except only the related AE is included (excluding the related reactogenicity reported within 7 days after vaccination [Section 3.1.2]).

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

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

5. Any AE leading to study withdrawal after vaccination.

6. Any AE leading to death after vaccination.

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

8. Any protocol-specified AESI reported from vaccination throughout the substudy. The following are protocol-specified AESIs based on AE PTs:

    - Confirmed diagnosis of influenza.
    - Confirmed diagnosis of RSV infection.
    - Confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination. See PTs provided in Section 3.5.3.
    - Confirmed COVID-19 diagnosis after Visit 1 through the end of the study (clinical signs/symptoms per CDC[1] and positive SARS-CoV-2 NAAT or rapid antigen test result).

Variables 1 through 6 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 Endpoints

The secondary immunogenicity endpoints are similar to the primary immunogenicity endpoints except they are not applicable to Group 1 or Group 2.

3.3. Other Endpoints

3.3.1. Immunogenicity Results Fold Rise

As immunogenicity is measured both before vaccination and 1 month after vaccination, the fold rise of each assay result will be derived as the ratio of postvaccination results to prevaccination results for each participant. When calculating a fold rise, if assay results are < LLOQ, the assay results will be converted to 0.5 × LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to the LLOQ.

3.3.2. RSV A/B

RSV A/B NT will be derived for the geometric mean of RSV A and RSV B NTs measured at each blood sampling time point for each participant.

RSV A/B NT fold rise will be derived for the geometric mean of RSV A and RSV B NT fold rises from before vaccination to after vaccination for each participant.

3.3.3. HAI Seroprotection

HAI seroprotection is defined as an HAI titer ≥1:40. This will be derived for each participant at Visit A101 and Visit A102 for each strain.

3.3.4. HAI Seroconversion

HAI seroconversion from before vaccination to after vaccination (Visit A102) will be defined for each participant for each strain as follows:

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

3.3.5. SARS-CoV-2 Seroresponse

SARS-CoV-2 seroresponse after vaccination will be defined for each participant for each strain as follows:

- 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.

3.3.6. RSV Seroresponse

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.

3.4. Baseline Variables

3.4.1. 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.

3.4.2. Demographics, Baseline, and Medical History

The demographic variables that will be collected include sex, race, ethnicity, height, weight, and date of birth. Age at the time of vaccination (in years) will be derived based on birthday. For example, if the vaccination date is 1 day before the participant's 86th birthday, the participant is 85 years old. The standard unit (cm) for height should be used. All other nonstandard units should be converted to cm, rounded to 2 decimal places. Similarly, the standard unit of weight (kg) should be used. All other nonstandard units should be converted to kg, rounded to 2 decimal places. BMI will be derived as a ratio of body weight in kilograms (kg) to the square of the body height in meters (m) and rounded to 2 decimal places; the unit for BMI is kg/m^2.

The N-binding antibody test will be performed by the central laboratory on each blood sample to establish prior exposure to SARS-CoV-2 up to each time point.

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

3.4.3. E-Diary 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 of Day 1 through Day 7.
- E-diary data transmitted on any day of Day 1 through Day 7.

- E-diary data transmitted at 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 WHODD.

3.5. Safety Endpoints

3.5.1. Adverse Events

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

- Tier 1 events: These are prespecified events of clinical importance. As of this SAP amendment, no Tier 1 events have been identified for the combination vaccine. However, Guillain-Barre syndrome (occurring from Day 1 through Day 43 after vaccination), polyneuropathy (occurring from Day 1 through Day 43 after vaccination), and atrial fibrillation (occurring from vaccination through the 1-month follow-up visit) have been identified as Tier 1 events for RSVpreF. The RSV program Tier 1 list of MedDRA PTs is maintained by the Safety Risk Lead in the Custom Adverse Event Term List System (CAETeLiSt) and referenced in the Safety Surveillance Review Plan for the program. The current list of Tier 1 events referenced by this study for RSVpreF should be confirmed to ensure that appropriate Tier 1 events will be used to produce final tables/graphs before conducting an analysis.
- Tier 2 events: Considering this is a Phase 1/2 study with no placebo-controlled groups, no Tier 2 event will be defined.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.5.2. Vital Sign Data

The temperature collected before the vaccination will only be used to assess any potential protocol deviation for vaccination temporary delay. Similarly, pulse rate and seated blood pressure are collected to ensure that participants meet eligibility for vaccination. Therefore, these will not be included as a baseline variable.

3.5.3. 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 must be specifically evaluated. ECG and measurement of troponin will be performed locally for further 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. AE PTs will be used to determine if these cases are AESIs or not.

The following variables will be derived for these assessments and the derivation will be based on AE PTs:

Cases	Derivation
Cases reported as myocarditis or pericarditis (AESIs)	AE PT included in "autoimmune myocarditis," "autoimmune pericarditis," "carditis," "chronic myocarditis," "eosinophilic myocarditis," "giant cell myocarditis," "hypersensitivity myocarditis," "immune-mediated myocarditis," "immune-mediated pericarditis," "myocarditis," "myopericarditis," "pericarditis," "pericarditis adhesive," "pericarditis constrictive," or "pleuropericarditis" with symptom onset within 28 days after vaccination.
Cardiac illness visits only (potential myocarditis/pericarditis only)	AE PT not above, but with a nonmissing signs and symptoms page with symptom onset within 28 days after vaccination.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

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

Participant Analysis Set	Description	Applicable Analysis
Enrolled	All participants who sign the ICD.	Study conduct such as participant disposition
Randomized population	All participants who are assigned a randomization number in the IWRS regardless of whether or not the study intervention was administered.	Immunogenicity analysis population disposition
Safety population	All participants who receive the study intervention.	AE/SAE analysis

Participant Analysis Set	Description	Applicable Analysis
E-diary safety population	All participants who receive 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.	Local reactions and systemic events analysis
mITT immunogenicity population	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.	Supplementary analysis on primary/secondary immunogenicity endpoints
Evaluable immunogenicity population	All participants randomized in Substudy A who meet the following criteria: • Are eligible for this substudy. • Received study intervention(s) to which they were randomized. • Had the 1-month postvaccination blood collection within 27 to 42 days after vaccination. • Had no major protocol violations from vaccination randomization through the 1-month postvaccination blood draw. • Had at least 1 valid and determinate assay result 1 month after vaccination.	Primary analysis population for immunogenicity endpoints (primary/secondary/exploratory)

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Both primary and secondary immunogenicity objectives are hypothesis testing objectives. The subsections below describe details of hypotheses to be tested for each objective.

5.1.1. Statistical Hypotheses for Combined Vaccine Coadministered With QIV

A total of 8 hypotheses will be tested for the first primary immunogenicity objective as described below for each vaccine component.

1. The null hypothesis (H_0) to assess noninferiority with respect to RSVpreF will be evaluated by the following hypothesis for both RSV A and RSV B as measured by NT:

   H_0: $\ln(\mu_1) - \ln(\mu_4) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority, and $\ln(\mu_1)$ and $\ln(\mu_4)$ are the natural log of the geometric mean of NT 1 month after vaccination for Group 1 and Group 4, respectively.

2. The null hypothesis (H_0) to assess noninferiority with respect to BNT162b2 will be evaluated by the following hypothesis for both SARS-CoV-2 Omicron BA.4/BA.5 strain and reference strain as measured by NT:

   H_0: $\ln(\mu_1) - \ln(\mu_3) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority, and $\ln(\mu_1)$ and $\ln(\mu_3)$ are the natural log of the geometric mean of NT 1 month after vaccination for Group 1 and Group 3, respectively.

3. The null hypothesis (H_0) to assess noninferiority with respect to QIV will be evaluated by the following hypothesis for each of the 4 strains included in QIV as measured by HAI titer:

   H_0: $\ln(\mu_1) - \ln(\mu_5) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority, and $\ln(\mu_1)$ and $\ln(\mu_5)$ are the natural log of the geometric mean of HAI titers 1 month after vaccination for Group 1 and Group 5, respectively.

5.1.2. Statistical Hypotheses for Combined Vaccine Alone

A total of 4 hypotheses will be tested for the second primary immunogenicity objective as described below for each vaccine component.

1. The null hypothesis (H_0) to assess noninferiority with respect to RSVpreF will be evaluated by the following hypothesis for both RSV A and RSV B as measured by NT:

   H_0: $\ln(\mu_2) - \ln(\mu_4) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority and $\ln(\mu_2)$ and $\ln(\mu_4)$ are the natural log of the geometric mean of NT 1 month after vaccination for Group 2 and Group 4, respectively.

2. The null hypothesis (H_0) to assess noninferiority with respect to BNT162b2 will be evaluated by the following hypothesis for both SARS-CoV-2 Omicron BA.4/BA.5 strain and reference strain as measured by NT:

   H_0: $\ln(\mu_2) - \ln(\mu_3) \leq \ln(0.5)$

   where ln(0.5) corresponds to a 2-fold margin for noninferiority and $\ln(\mu_2)$ and $\ln(\mu_3)$ are the natural log of the geometric mean of NT 1 month after vaccination for Group 2 and Group 3, respectively.

5.1.3. Statistical Hypotheses for Coadministration of 3 Individual Vaccines

A total of 8 hypotheses will be tested for the first of the secondary immunogenicity objectives, similar to Section 5.1.1, except Group 1 will be replaced with Group 7.

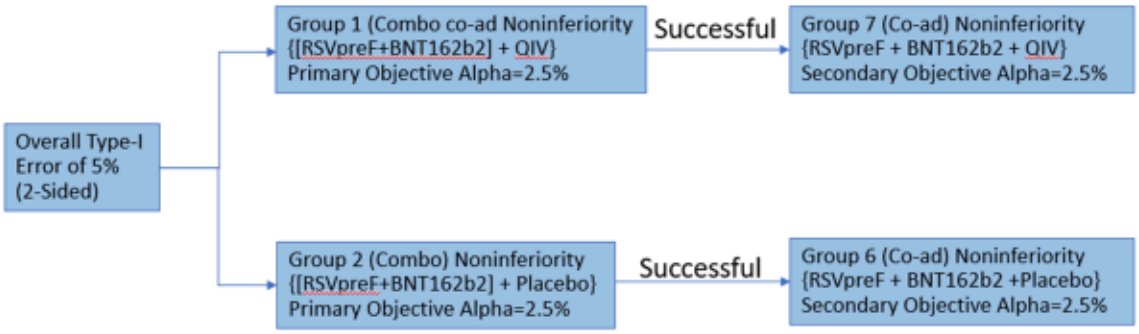
5.1.4. Statistical Hypotheses for Coadministration of 2 Individual Vaccines

A total of 4 hypotheses will be tested for the second of the secondary immunogenicity objectives, similar to Section 5.1.2, except Group 2 will be replaced with Group 6.

5.1.5. Multiplicity Adjustment

Type I error of 5% is equally split between the 2 primary immunogenicity objectives (2-sided 2.5% for each). The first primary immunogenicity objective will be achieved if all 8 null hypotheses are rejected. The second primary immunogenicity objective will be achieved if all 4 null hypotheses are rejected. The study is considered successful if either primary immunogenicity objective is achieved.

The secondary immunogenicity objectives will be tested sequentially after the primary objective(s) is achieved as described in the schema below.



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 study intervention 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 study intervention 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 Student t distribution, and then exponentiating the results.

5.2.2.2. Geometric Mean Fold Rises

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

5.2.2.3. 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.

5.2.2.5. 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 logarithm scale) to compare the immune response in the experimental group(s) with the reference group (individual vaccine alone). 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.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

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

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

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 (Days 1-7)" 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 to 6 days of e-diary data are transferred, it is expected that these reactogenicity events would be queried by the investigator for the missing e-diary days and entered in the AE CRF if any 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 assay results above LLOQ are considered accurate, and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis.

For calculating a fold rise, < LLOQ will be converted to 0.5 × LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only 1 of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

The LLOQs for each assay will be included in the final released assay data.

Values for sera that are designated as QNS, indeterminate results, or values recorded as "not done" will be set to "missing." Additionally, any time point with no blood draws will not be included in the analysis. No imputation will be done for these missing values, as MCAR is assumed for immunogenicity data according to Scott and Hsu.[4]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoints for Combined Vaccine Coadministered With QIV (Group 1) Noninferiority Objective

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.1.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: Final analysis of immunogenicity objective.
- 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 methodology: GMR, defined as the ratio of all of the 8 strain/subgroup-specific serology results measured by RSV NT, SARS-CoV-2 NT, and HAI GMTs in Group 1 to that for single vaccine administered alone (eg, Groups 3, 4, and 5) at Visit A102 will be summarized along with the 97.5% CI (Section 5.2.2.3). Descriptive statistics, including sample size (n), and GMTs at Visit A102 will be presented for Group 1 as well as Groups 3, 4, and 5 (Section 5.2.2).
- RCDCs for each of the 8 strain/subgroup-specific serology results at Visit A102 measured by RSV NT, SARS-CoV-2 NT, and HAI titers will be plotted after vaccination for the applicable groups (eg, HAI titers for Group 1 vs Group 5).

6.1.1.2. Supplementary Analysis

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

6.1.2. Primary Immunogenicity Endpoints for Combined Vaccine (Group 2) Noninferiority Objective

6.1.2.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.1.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis timing: Final analysis of immunogenicity objective.
- 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 methodology: GMR, defined as the ratio of all of the 4 strain/subgroup-specific serology results measured by RSV NT and SARS-CoV-2 NT GMTs in Group 2 to that in single vaccine administered alone (eg, Groups 3 and 4) at Visit A102 will be summarized along with the 97.5% CI (Section 5.2.2.3). Descriptive statistics, including sample size (n), and GMTs at Visit A102 will be presented for Group 2 and Groups 3 and 4 (Section 5.2.2).
- RCDCs for each of the 4 strain/subgroup-specific serology results at Visit A102 measured by RSV NT and SARS-CoV-2 NT will be plotted after vaccination for the applicable groups (eg, RSV A NT for Group 2 vs Group 4).

6.1.2.2. Supplementary Analysis

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

6.1.3. Local Reactions and Systemic Events

Analyses of reactogenicity endpoints are based on the safety population that includes participants with any e-diary data reported after vaccination. Reactogenicity data (Section 3.1.2.1 and Section 3.1.2.2) will be summarized by vaccine group, according to the study interventions the participants actually received.

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.3.1).
- Analysis set: Reactogenicity safety population (only participants with at least 1-day e-diary data transferred are included in the calculation) (Section 5.3.1.1).
- 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: Final analysis of immunogenicity objective.
- Intercurrent events and missing data: All data collected are included; partially missing e-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 group (Section 5.2.1).
- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event throughout the 7 days will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.3.2. Supplementary Analysis

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.2.1 and Section 3.1.2.2, will be summarized per the supplementary analysis with the same analysis population:

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

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

6.1.3.3. Sensitivity Analysis

Two sensitivity analyses will be conducted:

- Maximum severity of reactogenicity is assessed on 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 and SAEs

AEs and SAEs will be summarized by vaccine group, according to the study interventions the participants actually received. 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 2.2.1.3.1, Section 2.2.1.3.2, and Section 2.2.1.3.3).
- Analysis set: Safety population (Section 4).
- Analysis timing: Final analysis of immunogenicity objective; final database release.
- Intercurrent events and missing data: All data collected are included.
- 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 (Section 5.2.1).
- Bar charts with the proportions of participants for each variable will be plotted for each group. The bars may be divided into relatedness categories to highlight the proportions of participants with related events.
- The main analysis would be based on AEs excluding the reactogenicity events that were reported in the AE CRF (except for SAEs) (Section 3.1.2.3).

6.1.4.2. Supplementary Analysis

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

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

6.1.4.3. 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 Endpoints

Analyses will be similar to the primary endpoint, except that Group 1 will be replaced with Group 7 and Group 2 will be replaced with Group 6.

6.3. Other Endpoints

6.3.1. GMTs and GMFRs

RSV A NTs, RSV B NTs, and RSV A/B NTs at Visit 101 and Visit A102 will be summarized with n, GMTs, and 95% CIs for Groups 1, 2, 4, 6, and 7. The fold rise of RSV A NTs, RSV B NTs, and RSV A/B NTs at Visit A102 will be summarized with n, GMFR, and the 95% CI for Groups 1, 2, 4, 6, and 7.

QIV strain-specific HAI titers at Visit 101 and Visit A102 will be summarized with n, GMTs, and 95% CIs for Groups 1, 5, and 7. The fold rise of QIV strain-specific HAI titers at Visit A102 will be summarized with n, GMFR, and the 95% CI for Groups 1, 5, and 7.

SARS-CoV-2 strain-specific NTs at Visit 101 and Visit A102 will be descriptively summarized with n, GMTs, and 2-sided 95% CIs for Groups 1, 2, 3, 6, and 7. The fold rise of SARS-CoV-2 strain-specific NTs at Visit 102 will be descriptively summarized with n, GMFRs, and 2-sided 95% CIs for Groups 1, 2, 3, 6, and 7.

6.3.2. HAI Seroprotection and HAI Seroconversion

Descriptive statistics, including the proportion (%) of participants with HAI seroprotection at Visit A101 and A102, HAI seroconversion at Visit A102, 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 Groups 1, 5, and 7 in the evaluable immunogenicity population.

6.3.3. SARS-CoV-2 NT Seroresponse

Descriptive statistics, including the proportion (%) of participants with SARS-CoV-2 strain-specific NT seroresponse at Visit A102, 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 Groups 1, 2, 3, 6, and 7 in the evaluable immunogenicity population.

6.3.4. RSV NT Seroresponse

Descriptive statistics, including the proportion (%) of participants with RSV A NT seroresponse and RSV B NT seroresponse at Visit A102, 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 Groups 1, 2, 4, 6, and 7 in the evaluable immunogenicity population.

6.3.5. Additional Analysis

6.3.5.1. Descriptive Between-Group Comparisons

GMRs on RSV A NTs, RSV B NTs, and SARS-CoV-2 strain-specific NTs will be descriptively compared between Group 1 and Group 2 to explore potential coadministration of QIV interference to the combination vaccine immune response.

GMRs on RSV A NTs, RSV B NTs, and SARS-CoV-2 strain-specific NTs will be descriptively compared between Group 7 and Group 6 to explore immune response from coadministration of RSVpreF with BNT162b2, with or without QIV coadministration.

GMRs on RSV A NTs, RSV B NTs, and SARS-CoV-2 strain-specific NTs will be descriptively compared between Group 2 and Group 6 to explore immune response differences between the combination vaccine (1 injection) and coadministration of RSVpreF with BNT162b2.

GMRs on RSV A NTs, RSV B NTs, QIV strain-specific HAI titers, and SARS-CoV-2 strain-specific NTs will be descriptively compared between Group 1 and Group 7 to explore immune response differences.

All of these descriptive comparisons of GMRs will be summarized with 95% CIs.

6.3.5.2. Sensitivity Analysis

RSV A NTs and RSV B NTs at Visit A102 will be summarized with n, GMTs, and 95% CIs for Groups 1, 2, 6, 7, and 4. Using Group 4 as reference, GMR will be summarized with 95% CI. Model-adjusted LS GMTs and LS GMRs (to Group 4) with associated 95% CIs will be based on data from all 5 groups using the ANCOVA model (Section 5.2.2.5).

SARS-CoV-2 strain-specific NTs at Visit A102 will be summarized with n, GMTs, and 95% CIs for Groups 1, 2, 6, 7, and 3. Using Group 3 as reference, GMR will be summarized with 95% CI. Model-adjusted LS GMTs and LS GMRs (to Group 3) with associated 95% CIs will be based on data from all 5 groups using the ANCOVA model (Section 5.2.2.5).

QIV strain-specific HAIs at Visit A102 will be summarized with n, GMTs, and 95% CIs for Groups 1, 7, and 5. Using Group 5 as reference, GMR will be summarized with 95% CI. Model-adjusted LS GMTs and LS GMRs (to Group 5) with associated 95% CIs will be based on data from all 3 groups using the ANCOVA model (Section 5.2.2.5).

6.3.5.3. Combined Group 1 and Group 2 Analysis

If both primary objectives are achieved (LBCI >0.5) but the lower bound is <0.667, Group 1 and Group 2 will be combined to assess combination vaccine [RSVpreF+BNT162b2] immune response. In this analysis, the combined group will be compared with Groups 3 and 4 for the following:

- 95% CI for the GMT ratio (GMT combination/GMT RSVpreF alone) for RSV subgroup A and RSV subgroup B
- 95% CI for the GMT ratio (GMT combination/GMT bivalent BNT162b2 alone) for each COVID-19 strain
- 95% CI for the difference in proportions (combination minus RSVpreF alone) of participants achieving seroresponse for RSV subgroup A and RSV subgroup B
- 95% CI for the difference in proportions (combination minus bivalent BNT162b2 alone) of participants achieving seroresponse

6.4. Subset Analyses

No subset analysis is planned.

6.5. Baseline and Other Summaries and Analyses

For each vaccine group (Group 1 to 7), descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, ethnicity, height, weight, and BMI) and prior exposure to SARS-CoV-2 measured by the N-binding assay 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.

6.5.1. Study Conduct and Participant Disposition

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

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

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

For all of the AEs categorized in Section 3.1.2.3, each individual AE will be categorized by MedDRA and descriptively summarized by vaccine group.

AEs are classified into 1 of 3 tiers (Section 3.5.1). For Tier 1 events, 2-sided 95% CIs for the difference between the comparator group and reference group in the percentage of participants reporting the events, based on the Miettinen and Nurminen[3] method, will be provided. In addition, 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. The analysis on Tier 1 events is planned for comparing Groups 4, 6, and 7 pooled (RSVpreF coadministered or administered alone) and Groups 1, 2, 4, 6, and 7 pooled (RSVpreF combination or coadministered or administered alone), to Groups 3 and 5 pooled (Bivalent BNT162b2 or QIV administered alone, reference group).

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

6.6.2. Myocarditis or Pericarditis

The variable derived in Section 3.5.3 will be summarized with count, percentage, and 95% CI for each vaccine group.

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

7. INTERIM ANALYSES

7.1. Introduction

7.1.1. Analysis Timing

No formal interim analysis will be conducted for this study phase.

The primary analysis will be performed on safety and immunogenicity data through 1-month postvaccination visit (ie, Visit A102); all type I error will be spent at this analysis. Once this analysis has been completed, study participants and the study team may be unblinded to study intervention allocation. The 6-month safety data will be summarized when they become available.

7.1.2. Blinding and Unblinding

As described in Section 3.1.1, an unblinded statistician will send the barcode listings to sample management for specific assay testing.

8. REFERENCES

1 CDC. Symptoms of COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Updated: 26 Oct 2022. Accessed: 09 Feb 2023.

2 Newcombe RG. Two-sided confidence 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 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
BMI	body mass index
BNT162b2	Pfizer's COVID-19 vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
FDA	Food and Drug Administration (United States)
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
H1N1	influenza A virus
H3N2	influenza A virus subtype H3N2
HAI	hemagglutination inhibition assay
ICD	informed consent document
ID	identification
IWRS	interactive Web-based response system
LBCI	lower bound of the confidence interval
LLOQ	lower limit of quantitation
LS	least square
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
NT	neutralizing titer
Omi	Omicron
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient

Abbreviation	Term
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
[RSVpreF+BNT162b2]	combination RSVpreF and bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Document Approval Record

Document Name:	C5481001 Substudy A Statistical Analysis Plan V3 Clean Copy, 01 AUG 2023
Document Title:	A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED VACCINE CANDIDATE(S) AGAINST INFECTIOUS RESPIRATORY ILLNESSES, INCLUDING COVID-19 AND RSV, IN HEALTHY INDIVIDUALS – SUBSTUDY A

Signed By:	Date(GMT)	Signing Capacity
PPD	01-Aug-2023 20:07:21	Final Approval