Protocol C5261002

A PHASE 3, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A COMBINED MODIFIED RNA VACCINE CANDIDATE AGAINST COVID-19 AND INFLUENZA IN HEALTHY INDIVIDUALS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 16 May 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 28 Feb 2024	Protocol amendment 1 12 Jan 2024	N/A	N/A
2/ 16 May 2024	Protocol amendment 2 11 Apr 2024	• Included changes from protocol amendment 2 [redacted] • Included minor updates regarding the supplementary/sensitivity and subset analyses. • Included other minor updates for clarity throughout.	• Sections 2.2, 3.1.2, 5.1, and 6.1.2. Removed the NI objectives, estimands, and endpoints to demonstrate NI objectives in Cohort 1. • Sections 2.2, 3.2, 5.1, and 6.2.1. Added immunogenicity secondary objectives, estimands, and endpoints to demonstrate NI objectives in Cohort 3. • Sections 2.2, 3.2, 5.1, and 6.2.1. Added immunogenicity secondary objectives, estimands, and endpoints to demonstrate superiority objectives in Cohort 2. • Section 2.3. Updated the study design and added Cohort 3. • Section 5.1. Removed the hypotheses in Cohort 1 and added the hypotheses for the secondary objectives in Cohort 2 and Cohort 3. • Section 5.1.1. Updated the multiplicity adjustment rules based on the new hypothesis testing. • Section 6.4. Updated the subset analysis factors. • Section 7.2.1. Updated the analysis timings.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C5261002.

2.1. Modifications to the Analysis Plan Described in the Protocol

There is no modification to the analysis plan described in the protocol.

2.2. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in the table below.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population. These estimands estimate the immune response after study intervention administration in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. The estimands address the objective of estimating the maximum potential difference between 2 vaccine groups of the target population, since the impact of noncompliance is likely to diminish the observed difference between the 2 compared vaccine groups. Missing immunogenicity results will not be imputed. Immunogenicity results that are below the LLOQ will be handled as described in Section 5.3. Immunogenicity data after a postbaseline new onset of influenza or SARS-CoV-2 infection will be excluded from the analysis of the related immunogenicity endpoints using the evaluable immunogenicity population.

The estimands to evaluate the safety objective are based on the safety population. These estimands estimate vaccine safety after receipt of the study intervention. Partial missing AE start dates will be handled according to Pfizer safety rules (see Section 5.3). In general, completely missing reactogenicity data (ie, all 7 days of collection are regarded as missing) will not be imputed. For the partially missing reactogenicity data (ie, 1 to 6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.

Type	Objectives	Endpoints	Estimands
Primary (Safety)	To describe the safety and tolerability of study interventions in healthy participants 18 through 64 years of age	• Local reactions (pain at the injection site, redness, and swelling) in the right deltoid only • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	The percentage of participants 18 through 64 years of age receiving at least 1 dose of study intervention reporting: • Local reactions for up to 7 days following vaccination in the right deltoid only • Systemic events for up to 7 days following vaccination • AEs from vaccination through 4 weeks after vaccination • SAEs from vaccination through 6 months after vaccination

Type	Objectives	Endpoints	Estimands
Primary (Immunogenicity)	To demonstrate that the HAI immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) (Cohort 2)	• HAI titers (from HAI based on CCI -derived virus) for the matched seasonal strains (CCI) recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) • The difference in percentage of participants with seroconversion[a] to the seasonal strain (CCI) at 4 weeks after vaccination between participants who received CCI /BNT162b2 (Omi XBB.1.5) and those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5)
Primary (Immunogenicity)	To demonstrate that the SARS-CoV-2 immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV (Cohort 2)	• SARS-CoV-2 (Omi XBB.1.5)–neutralizing titers	In evaluable immunogenicity participants: • GMR of SARS-CoV-2–neutralizing titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV • The difference in percentage of participants with seroresponse[b] to SARS-CoV-2 (Omi XBB.1.5) strain at 4 weeks after vaccination between participants who received CCI /BNT162b2 (Omi XBB.1.5) and those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV

Type	Objectives	Endpoints	Estimands
Secondary (Immunogenicity)	To demonstrate that the HAI immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by QIV alone (Cohort 3)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV alone
Secondary (Immunogenicity)	To demonstrate that the SARS-CoV-2 immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by BNT162b2 (Omi XBB.1.5) alone (Cohort 3)	• SARS-CoV-2 (Omi XBB.1.5)– neutralizing titers	In evaluable immunogenicity participants: • GMR of SARS-CoV-2–neutralizing titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) alone
Secondary (Immunogenicity)	To demonstrate that the HAI immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) is noninferior to that elicited by CCI alone (Cohort 3)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received CCI alone
Secondary (Immunogenicity)	To demonstrate that the HAI immune response elicited by CCI BNT162b2 (Omi XBB.1.5) is superior to that elicited by QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) (Cohort 2)	• HAI titers (from HAI based on CCI derived virus) for the matched seasonal strains (CCI) recommended by WHO	In evaluable immunogenicity participants: • GMR of HAI titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5) • The difference in percentage of participants with seroconversion[a] to the seasonal strain (CCI at 4 weeks after vaccination between participants who received CCI /BNT162b2 (Omi XBB.1.5) and those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5)

Type	Objectives	Endpoints	Estimands
CCI			

Type	Objectives	Endpoints	Estimands
CCI			

a. Seroconversion is defined as having an HAI titer <1:10 prior to vaccination and ≥1:40 at the postvaccination time point of interest, or an HAI titer of ≥1:10 prior to vaccination with a minimum 4-fold rise at the postvaccination time point of interest.
b. Seroresponse is defined as achieving a postvaccination ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

2.3. Study Design

This is a Phase 3, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of selected CCI when administered in combination with BNT162b2 (Omi XBB.1.5) compared to a licensed inactivated QIV administered in the deltoid opposite to that used for administration of BNT162b2 (Omi XBB.1.5) in healthy adults 18 through 64 years of age. Additionally, the study will evaluate CCI administered in combination with BNT162b2 (Omi XBB.1.5) in comparison to standalone administration of QIV, CCI and BNT162b2 (Omi XBB.1.5). The vaccine candidates are divided into cohorts, where approximately 8550 total participants 18 through 64 years of age will be enrolled into 1 of 3 cohorts:

Cohort 1: Approximately 450 participants randomized in a 2:1 ratio by site-based randomization to 1 of the following:

- **Arm A:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid and placebo administered in the left deltoid, concurrently.
- **Arm B:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid and licensed QIV (CCI) administered in the left deltoid, concurrently.

Enrollment of Cohort 1 will be paused in the IRT system after the randomization of approximately 450 participants into Cohort 1. Safety data (including e-diary data, SAEs, AEs, and AESIs) of approximately 450 vaccinated participants will be evaluated by the EDMC after 60 days CCI

CCI

Cohort 2: Approximately 4500 participants randomized in a 2:1 ratio by site-based randomization to 1 of the following:

- **Arm C:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid and placebo administered in the left deltoid, concurrently.
- **Arm D:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid and licensed QIV CCI) administered in the left deltoid, concurrently.

Cohort 3: Approximately 3600 participants 18 through 64 years of age will be enrolled and randomized in a 2:2:1:1 ratio by site-based randomization to 1 of the following:

- **Arm E:** CCI /BNT162b2 (Omi XBB.1.5) administered in the right deltoid.
- **Arm F:** 30 µg BNT162b2 (Omi XBB.1.5) administered in the right deltoid.
- **Arm G:** licensed QIV CCI) administered in the right deltoid.
- **Arm H:** CCI administered in the right deltoid.

Prespecified local reaction and systemic event data will be collected in an e-diary for 7 days, or longer for ongoing symptoms, after study intervention administration (ie, from Day 1, the day of vaccination, until symptom resolution). Blood samples of approximately 20 mL will be collected for immunogenicity assessments prior to vaccination and at 4 weeks and 6 months after vaccination.

CCI

Following vaccination, AEs will be collected from informed consent signing through Visit 2, and SAEs will be collected from informed consent signing through Visit 3. In addition, AEs occurring up to 48 hours after blood draws that are related to study procedures will also be collected and for collection of AESIs refer to Section 8.4.8 of the protocol.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Safety Endpoints

In participants receiving at least 1 dose of study intervention, the safety primary endpoints are as follows:

- Local reactions (redness, swelling, and pain at the injection site) for up to 7 days following vaccination in the right deltoid only.
- Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following vaccination.
- AEs from vaccination through 4 weeks after vaccination.
- SAEs from vaccination through 6 months after vaccination.

3.1.1.1. Local Reactions and Systemic Events

The local reactions, including redness, swelling, and pain at the injection site, are reported in the e-diary and/or CRF from Day 1 through Day 7 after study vaccination, where Day 1 is the day of vaccination. Local reactions will be assessed at the injection site on the right deltoid only after vaccinations given at Visit 1. This section describes derivations with details for the assessment of reactogenicity data: presence of event, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 2 defines the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of study vaccination.

Table 2. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable	Yes (1)	No (0)
Presence of each local reaction on any day	Participant reports the reaction as "yes" on any day (Day 1 through Day 7)	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7)
Presence of any local reaction on any day	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7)	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7)

Note: Completely missing reactogenicity data will not be imputed. Participants with no reactogenicity data reported will not be included in the reactogenicity summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 3. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 3.

Table 3. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain

Table 3. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.
b. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor. Grade 4 local reactions will be collected on the CRF.

For each local reaction or systemic event after vaccination, the maximum severity grade will be derived for the collection period (Day 1 through Day 7, where Day 1 is the day of vaccination) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive (last day of reaction − first day of reaction + 1), after vaccination. The resolution day is defined as the last day on which the reaction or event is recorded in the e-diary or CRF. For a reaction or event collected in multiple sources, the earliest start date and the latest end date will be used in calculating duration. If there is no known resolution/end date, the duration will be reported as "unknown" and set to "missing."

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting a reaction of any severity after vaccination. Change in severity during the event does not impact the originally determined onset day. For example, for the onset day of each local reaction, if participants report a change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

For a reaction collected in multiple sources, the earliest date of reporting the reaction will be used in calculating the onset day.

3.1.1.2. Systemic Events

The systemic events, including vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain, are assessed and recorded in the e-diary and/or CRF from Day 1 through Day 7, where Day 1 is the day of vaccination. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed as mild, moderate, or severe according to the grading scale in Table 4.

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

a. If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.
b. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 systemic events will be collected on the CRF.

3.1.1.3. Fever

Temperatures will be taken orally. Temperature will be collected in the reactogenicity e-diary daily for 7 days or longer following vaccination (where Day 1 is the day of vaccination). It will also be collected at any time during the reactogenicity e-diary data collection period when fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C (<95°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 5.

Table 5. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

3.1.1.4. Use of Antipyretic/Pain Medication

The use of antipyretic/pain medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of vaccination. For the use of antipyretic/pain medication from Day 1 through Day 7, the following endpoints and variables will be derived:

- Presence (yes or no) of use of antipyretic/pain medication on each day (Day 1 through Day 7)
- Presence (yes or no) of use of antipyretic/pain medication on any day (Day 1 through Day 7)
- Duration (first to last day reported) of use of antipyretic/pain medication
- Onset day of use of antipyretic/pain medication

The use of antipyretic/pain medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.5. Adverse Events

AEs are collected from the completion of informed consent through 4 weeks (Visit 2) after study vaccination. SAEs are collected from the completion of informed consent through 6 months after study vaccination (Visit 3). Additionally, any AEs occurring up to 48 hours after a blood draw must be recorded. AEs/SAEs will be categorized according to MedDRA terms.

The safety primary endpoints "AEs from vaccination through 4 weeks after vaccination" and "SAEs from vaccination through 6 months after vaccination" will be summarized, by SOC and PT, at the participant level for each vaccine group within each cohort.

These safety primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol). Partially missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

3.1.2. Immunogenicity Endpoints

In Cohort 2 participants who receive the study intervention (CCI BNT162b2 or QIV administered concomitantly with BNT162b2 [Omi XBB.1.5]):

- HAI titers (from HAI based on CCI derived virus) for each matched seasonal strain (CCI recommended by WHO at 4 weeks after study vaccination.
- SARS-CoV-2 (Omi XBB.1.5)–neutralizing titers at 4 weeks after study vaccination.

3.2. Secondary Endpoint(s)

In Cohort 3 participants who receive the study intervention (CCI BNT162b2, QIV alone, or CCI alone):

- HAI titers (from HAI based on CCI derived virus) for each matched seasonal strain CCI recommended by WHO at 4 weeks after study vaccination.

In Cohort 3 participants who receive the study intervention (CCI BNT162b2 or BNT162b2 [Omi XBB.1.5] alone):

- SARS-CoV-2 (Omi XBB.1.5)–neutralizing titers at 4 weeks after study vaccination.

In Cohort 2 participants who receive the study intervention (CCI BNT162b2 or QIV administered concomitantly with BNT162b2 [Omi XBB.1.5]):

- HAI titers (from HAI based on CCI derived virus) for each matched seasonal strain CCI recommended by WHO at 4 weeks after study vaccination.

3.3. Other Safety Endpoint(s)

All safety endpoints are described in Section 3.1.1.

CCI

CCI

[redacted]

3.5. Baseline Variables

3.5.1. Demographics and Medical History

The demographic variables are age, sex (male or female), race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, and not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported).

For reporting of race, where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Medical history will be categorized according to MedDRA.

3.5.2. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic/pain medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Ongoing medications, if taken, will be recorded and include start date, name of the medication, dose, unit, route, and frequency at Visit 1.
- All prior receipt of any COVID-19 vaccine.

- Date of licensed or investigational influenza vaccine within the 3 years prior to enrollment.
- Any vaccinations received from 28 days prior to Visit 1 until the last visit (Visit 3).
- Prohibited medications listed in Section 6.9.1 of the protocol, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.
- Details of any concomitant medication taken to treat any prespecified local or systemic reactogenicity symptoms reported in the e-diary will be collected.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in Table 6. 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.

Table 6. Analysis Sets Description

Participant Analysis Set	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All randomized participants who are eligible, receive the study intervention to which they were randomized, have at least 1 valid and determinate immunogenicity result from the blood sample collected within 27 to 42 days after vaccination, and have no major protocol violations. Participants will be grouped according to the vaccine as randomized in the analysis based on the evaluable immunogenicity population.
mITT immunogenicity	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination. Participants will be grouped according to the vaccine as randomized in the analysis based on the mITT immunogenicity population.
Safety	All participants who receive at least 1 dose of the study intervention. Participants will be grouped according to the vaccine as administered in the analysis based on the safety population.

For determination of the evaluable immunogenicity population(s), major protocol violations will be determined by the medical monitor. A major protocol violation is a protocol violation that, in the opinion of the sponsor clinician, would materially affect assessment of immunogenicity, eg, participant's receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor clinician will identify those participants with a protocol violation prior to unblinding of the study.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. The SAP may modify what is outlined in the protocol, where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

5.1. Hypotheses and Decision Rules

Two immunogenicity primary objectives and 4 immunogenicity secondary objectives have been defined for this study. The immunogenicity primary (Cohort 2) and secondary (Cohort 3) objectives involve a demonstration of NI of the immune responses measured 4 weeks after study intervention administration, and the immunogenicity secondary (Cohort 2) objective involves a demonstration of superiority of the immune responses measured 4 weeks after study intervention administration, as detailed below.

The immunogenicity primary objectives (Cohort 2) are to demonstrate NI of the immune response to CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV for all targeted strains (seasonal strains CCI] recommended by WHO and the SARS-CoV-2 Omi XBB.1.5 strain).

The first immunogenicity secondary objective (Cohort 3) is to demonstrate NI of the HAI immune response for the matched seasonal influenza strains recommended by WHO (CCI elicited by CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to QIV alone.

The second immunogenicity secondary objective (Cohort 3) is to demonstrate NI of the SARS-CoV-2 immune response elicited by CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) alone.

The third immunogenicity secondary objective (Cohort 3) is to demonstrate NI of the HAI immune response for the matched seasonal influenza strains recommended by WHO CCI) elicited by CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to CCI alone.

The fourth immunogenicity secondary objective (Cohort 2) is to demonstrate superiority of the HAI immune response to CCI /BNT162b2 (Omi XBB.1.5) at 4 weeks after vaccination compared to BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV for all targeted strains CCI) recommended by WHO.

For evaluation of the immunogenicity primary objectives (Cohort 2), 2 statistical hypotheses for each targeted strain will be defined as described below:

$$H_{01}: \ln(\mu_1) - \ln(\mu_2) \leq \ln(\text{CCI}),$$

Where ln(CCI) corresponds to a CCI margin for NI, and μ_1 and μ_2 are the GMTs from Arm C and Arm D, respectively, measured 4 weeks after vaccination.

$$H_{02}: \pi_1 - \pi_2 \leq \text{CCI}\%,$$

where π_1 and π_2 are the proportions of participants achieving seroconversion or seroresponse at 4 weeks after vaccination for Arm C and Arm D, respectively.

For evaluation of immunogenicity secondary objectives (Cohort 3), 1 statistical hypothesis for each target strain will be defined as described below:

$$H_{01}: \ln(\mu_1) - \ln(\mu_2) \leq \ln(\text{CCI}),$$

where ln(CCI) corresponds to a CCI margin for NI and μ_1 and μ_2 are the geometric mean of titers in Arm E and the corresponding comparative vaccine (Arm F and Arm G and Arm H) groups, respectively, measured 4 weeks after vaccination.

For evaluation of the immunogenicity secondary objective (Cohort 2), 2 statistical hypotheses for each targeted seasonal strain (CCI recommended by WHO) will be defined as described below:

$$H_{01}: \ln(\mu_1) - \ln(\mu_2) \leq \ln(\text{CCI}),$$

where ln(1) corresponds to a CCI margin for superiority and μ_1 and $\mu_2$are the geometric mean of titers from Arm C and Arm D, respectively, measured at 4 weeks after vaccination.

$$H_{02}: \pi_1 - \pi_2 \leq \text{CCI}\%,$$

where π_1 and π_2 are the proportions of participants achieving seroconversion at 4 weeks after vaccination for Arm C and Arm D, respectively.

For each strain, NI based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is CCI NI based on seroconversion or seroresponse (Cohort 2 only) will be declared if the lower limit of the 2-sided 95% CI for the difference in percentage of participants achieving seroconversion or seroresponse is greater than CCI%; superiority (Cohort 2 only) based on GMR will be declared if the lower limit of the 2 sided 95% CI for the GMR is CCI; superiority based on seroconversion (Cohort 2 only) will be declared if the lower limit of the 2-sided 95% CI for the difference in percentage of participants achieving seroconversion is CCI%.

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5.1.1. Multiplicity Adjustment

Hypothesis testing of the objectives for Cohort 2 (2 immunogenicity primary objectives and the fourth secondary objective) will be evaluated independently from that of Cohort 3 (3 immunogenicity secondary objectives) without applying any multiplicity adjustment. CCI

Within Cohort 2, the immunogenicity primary objectives and the fourth secondary objective will be evaluated sequentially. The immunogenicity primary endpoints/estimands are considered coprimary. There are CCI hypothesis tests (CCI) for the immunogenicity primary NI objectives (CCI /BNT162b2 [Omi XBB.1.5] vs BNT162b2 [Omi XBB.1.5] administered concomitantly with QIV), with 2 statistical hypotheses for each of the CCI targeted influenza and SARS-CoV-2 strains. Each hypothesis will be tested at a 1-sided alpha level of 0.025. The immunogenicity primary objectives will be achieved if NI is met for all CCI statistical hypotheses. After the immunogenicity primary NI objectives (Cohort 2) are established, the CCI statistical hypotheses for the fourth secondary objective (Cohort 2) will be tested sequentially in the following order of CCI seasonal influenza strains: CCI and the hypothesis will be tested first based on GMR and then based on the seroconversion rate for each strain. Therefore, the overall type I error rate within Cohort 2 is fully controlled.

Within Cohort 3, the 3 immunogenicity secondary objectives will be evaluated sequentially in the following order: comparing CCI /BNT162b2 (Omi XBB.1.5) with QIV for CCI targeted influenza strains, CCI BNT162b2 (Omi XBB.1.5) with BNT162b2 (Omi XBB.1.5) for the SARS-CoV-2 Omi XBB.1.5 strain, and CCI /BNT162b2 (Omi XBB.1.5) with CCI for CCI targeted influenza strains. There are CCI hypothesis tests for the immunogenicity secondary NI objectives (CCI /BNT162b2 [Omi XBB.1.5] vs QIV for CCI targeted influenza strains, 1 for CCI /BNT162b2 [Omi XBB.1.5] vs BNT162b2 [Omi XBB.1.5] for the SARS-CoV-2 Omi XBB.1.5 strain, and CCI /BNT162b2 [Omi XBB.1.5] vs CCI for CCI targeted influenza strains). Each hypothesis will be tested at a 1-sided alpha level of 0.025. For objectives involving hypotheses for CCI influenza strains, all CCI hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error within Cohort 3 is fully controlled.

5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. The safety data will be summarized within each cohort but may also be summarized descriptively across cohorts.

For all the immunogenicity endpoints, the analysis will be primarily based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT immunogenicity population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations.

5.2.1. Analyses for Binary Endpoints

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

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

Another approach to calculate the adjusted difference in seroresponse rate or seroconversion rate between the 2 vaccine groups and the associated 95% CI will be based on the Miettinen and Nurminen method stratified by baseline NT category (< median, ≥ median) and age group (< median, ≥ median). The median of baseline NTs and age will be calculated based on the pooled data in the 2 comparator groups.

Three-Tier Approach for AE Summary

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers:

1. Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; there is no Tier 1 event identified for the study interventions at this stage.

2. Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA PT is defined as a Tier 2 event if there are at least 1% of participants in at least 1 study arm reporting the event.

3. Tier 3 events are those that are neither Tier 1 nor Tier 2 events.

For both Tier 1 (if any are identified later) and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between the 2 comparison groups will be calculated using the Miettinen and Nurminen method.

In addition, for Tier 1 events (if any are identified later), the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events between the 2 comparison groups, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.

Descriptive summary statistics will be provided for Tier 3 events for each study arm.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Mean Titers

The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking logarithm transformations of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

5.2.2.2. Geometric Mean Ratio

Unadjusted GMR

The unadjusted GMR will be calculated as the difference in the means of logarithmically transformed assay results between 2 vaccine groups and exponentiating the difference. The 2-sided 95% CI will be obtained by exponentiating the limits of the CI for the mean difference of the logarithmically transformed assay results based on the t distribution.

Model-based GMR

The model-based GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on the analysis of logarithmically transformed assay results using a linear regression model that includes the baseline assay results (HAI titer/SARS-CoV-2 NT), age, and vaccine group as covariates.

5.2.2.3. Geometric Mean Fold Rises

Fold rises are defined as ratios of the results after vaccination to the results before vaccination. The calculations of fold rises are limited to participants with no missing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. 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.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will be plotted as a step function of the proportion of participants with the assay results equal to or exceeding a specified value over the full range of the observed assay results. 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

In general, completely missing reactogenicity data (ie, all 7 days of collection are missing) will not be imputed. For partially missing reactogenicity data (eg, 1 to 6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.

A partial AE start date (missing day, missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant. A completely missing start date for an AE is not allowed in data collection. No other missing information will be imputed in the safety analysis.

Values that are designated as serum QNS, indeterminate, or "not done" will be set to "missing." Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the calculation of GMCs/GMTs.

When calculating a fold rise, the assay results will be converted to 0.5 × LLOQ if assay results are < 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. If both the numerator and denominator are < LLOQ, then both will be converted to 0.5 × LLOQ.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions and Systemic Events

6.1.1.1.1. Main Analysis

- Estimand(s): Percentages of participants with local reactions and systemic events for up to 7 days after study vaccination (Section 3.1) in each vaccine group.
- Analysis set(s): Safety population (Section 4).
- Analysis time point(s): Day 1 through Day 7 after vaccination.
- Statistical method(s): Descriptive summary (Section 5.2).

- Intercurrent events and missing data: Missing data will be handled as described in Section 5.3.

- Reporting results: Descriptive summaries for each and any local reaction/systemic event after study vaccination will be presented, by maximum severity, for each vaccine group within each cohort. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Sensitivity/Supplementary Analyses

As supplementary analyses to support the assessment of local reactions and systemic events, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction or systemic event after vaccination.

- Onset day of each local reaction or systemic event after vaccination.

These continuous endpoints will be summarized by descriptive summary statistics (n, mean, median, standard deviation, minimum, and maximum) for each vaccine group within each cohort.

The use of antipyretic medication/pain (see Section 3.1.1.4) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the percentages of participants for each local reaction and each systemic event on any day (Day 1 through Day 7) will be plotted for each vaccine group within each cohort after vaccination. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Adverse Events

6.1.1.2.1. Main Analysis

- Estimand(s): Percentages of participants reporting AEs from vaccination through 4 weeks after vaccination, and percentages of participants reporting SAEs from vaccination through 6 months after vaccination (Section 3.1.1.5).

- Analysis set(s): Safety population (Section 4).

- Analysis time point(s): AEs from vaccination through 4 weeks after vaccination; SAEs from vaccination through 6 months after vaccination.

- Statistical method(s): 3-Tier approach for AEs as described in Section 5.2.1. Descriptive statistics for SAEs.

- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).

- Reporting results: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of AEs (from vaccination through 4 weeks after vaccination) and SAEs (from vaccination through 6 months after vaccination) will be provided for each vaccine group within each cohort.

For all 3 tiers, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants reporting any AE, for each SOC, and each PT within the SOC, will be presented by vaccine group.

For AEs classified as Tier 2 events, the differences in percentages between the 2 comparison groups (Arm A vs Arm B for Cohort 1, Arm C vs Arm D for Cohort 2, and Arm E vs each of the other 3 arms [Arm F, Arm G, and Arm H] for Cohort 3), and associated 2-sided 95% CIs, will be provided.

For Tier 1 events (if any are identified later), the difference in percentage, the associated 2-sided 95% CI for the percentage difference, and the asymptotic p-values will also be provided.

6.1.1.2.2. Sensitivity/Supplementary Analysis

To support the interpretation of the main analysis results, descriptive summary statistics will also be provided by vaccine group for related AEs, severe AEs, and protocol-specified AESIs (defined in Section 8.4.8 of the protocol).

Immediate AEs (within the first 30 minutes after vaccination) will also be descriptively summarized for each vaccine group if the number of immediate AEs is sufficiently large; otherwise, they may be listed only.

Symptoms and measurements collected at cardiac evaluation visits for monitoring of potential myocarditis or pericarditis will be presented in a listing, regardless of whether there is a confirmed diagnosis.

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All AEs that were collected before vaccination or more than 4 weeks after vaccination (outside of the reporting period) may not be included in the AE summary tables but will be included in the AE listings.

Figures:

A forest plot for the percentage differences and associated 2-sided 95% CIs of Tier 2 events may be presented.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Main Analysis

- Estimand(s) in Cohort 2:
  - GMR of HAI titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5).
  - The difference in percentage of participants with seroconversion to the seasonal strain at 4 weeks after vaccination between participants who received CCI BNT162b2 (Omi XBB.1.5) and those who received QIV administered concomitantly with BNT162b2 (Omi XBB.1.5).
  - GMR of SARS-CoV-2 (Omi XBB.1.5)–neutralizing titers at 4 weeks after vaccination in participants who received CCI BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV.
  - The difference in percentage of participants with seroresponse to the SARS-CoV-2 (Omi XBB.1.5) strain at 4 weeks after vaccination between participants who received CCI BNT162b2 (Omi XBB.1.5) and those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV.
- Analysis set(s): Evaluable immunogenicity population and mITT immunogenicity population (as applicable) (Section 4).
- Analysis time point(s): 4 Weeks after vaccination.
- Statistical method(s): Analysis will be performed within each cohort independently. The unadjusted GMR and the associated 2-sided 95% CIs will be provided using methods described in Section 5.2.2.2. The difference in percentage of participants with seroconversion/seroresponse, and the associated 2-sided 95% CIs, will be calculated using the Miettinen and Nurminen method (Section 5.2.1). Seroconversion is defined as having an HAI titer <1:10 prior to vaccination and ≥1:40 at the postvaccination time point of interest, or an HAI titer of ≥1:10 prior to vaccination with a minimum 4-fold rise at the postvaccination time point of interest. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is

below the LLOQ, the postvaccination measure of ≥4 × LLOQ will be considered seroresponse. NI based on the GMR will be established if the lower bound of the 2-sided 95% CI for the GMR is greater than CCI and NI based on the seroconversion/seroresponse rate difference will be established if the lower bound of the 2-sided 95% CI for the difference in percentage is greater than CCI%.

- Intercurrent events and missing data: Assay results below the LLOQ will be handled as specified in Section 5.3. Missing data will not be imputed. Assay data after a postbaseline new onset of influenza or SARS-CoV-2 infection will be excluded from the analysis of the related immunogenicity endpoint using the evaluable immunogenicity population.

- Reporting results: The unadjusted GMR and the associated 2-sided 95% CI, along with the GMTs and the associated 2-sided 95% CIs for each vaccine group, will be provided. The number/percentage of participants with seroconversion/seroresponse and the corresponding 95% CIs for each vaccine group, and the difference in percentage of participants with seroconversion/seroresponse between the 2 comparison groups and associated 2-sided 95% CIs, will be calculated.

6.1.2.2. Supplementary Analysis

Empirical RCDCs will be plotted separately for each strain by vaccine group. Bar charts with the numbers, proportions of participants achieving HAI seroconversion, SARS-CoV-2 seroresponse rate, and associated 95% CIs will be provided for each strain by vaccine group within each cohort. Further plots of GMTs and/or GMFRs may also be done.

Additional model-based GMRs and associated 95% CIs based on a linear regression model (as specified in Section 5.2.2.2) may also be provided. Adjusted difference in percentage of participants with seroconversion/seroresponse at 4 weeks after vaccination and the associated 2-sided 95% CIs may also be calculated using the statistical methods described in Section 5.2.1.

6.2. Secondary Endpoint(s)

6.2.1. Main Analysis

- Estimand(s) in Cohort 3:

  - GMR of HAI titers for each matched seasonal strain CCI at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received QIV alone.

  - GMR of SARS-CoV-2 (Omi XBB.1.5)–neutralizing titers at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) alone.

  - GMR of HAI titers for each matched seasonal strain CCI at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received CCI alone.

- Estimand(s) in Cohort 2:
  - GMR of HAI titers for each matched seasonal strain (CCI) at 4 weeks after vaccination in participants who received CCI /BNT162b2 (Omi XBB.1.5) to those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV.
  - The difference in percentage of participants with seroconversion to the seasonal strain (CCI) at 4 weeks after vaccination between participants who received CCI /BNT162b2 (Omi XBB.1.5) and those who received BNT162b2 (Omi XBB.1.5) administered concomitantly with QIV.
- Analysis set(s): Evaluable immunogenicity population and mITT immunogenicity population (as applicable) (Section 4).
- Analysis time point(s): 4 Weeks after vaccination.
- Statistical method(s): Analysis will be performed within each cohort independently. The unadjusted GMR and the associated 2-sided 95% CIs will be provided using methods described in Section 5.2.2.2. The difference in percentage of participants with seroconversion/seroresponse, and the associated 2-sided 95% CIs, will be calculated using the Miettinen and Nurminen method (Section 5.2.1).
- Intercurrent events and missing data: Assay results below the LLOQ will be handled as specified in Section 5.3. Missing data will not be imputed. Assay data after a postbaseline new onset of influenza or SARS-CoV-2 infection will be excluded from the analysis of the related immunogenicity endpoint using the evaluable immunogenicity population.
- Reporting results: The unadjusted GMR and the associated 2-sided 95% CI, along with the GMTs and the associated 2-sided 95% CIs for each vaccine group within each cohort, will be provided. The number/percentage of participants with seroconversion and the corresponding 95% CIs for each vaccine group, and the difference in percentage of participants with seroconversion between the 2 comparison groups within each cohort and associated 2-sided 95% CIs, will be calculated.

6.2.2. Supplemental Analysis

Empirical RCDCs will be plotted separately for each strain by vaccine group. Further plots of GMTs and/or GMFRs may also be done.

Additional model-based GMRs and associated 95% CIs based on a linear regression model (as specified in Section 5.2.2.2) may also be provided. The adjusted difference in percentage of participants with seroconversion at 4 weeks after vaccination and the associated 2-sided 95% CIs may also be calculated using the statistical methods described in Section 5.2.1.

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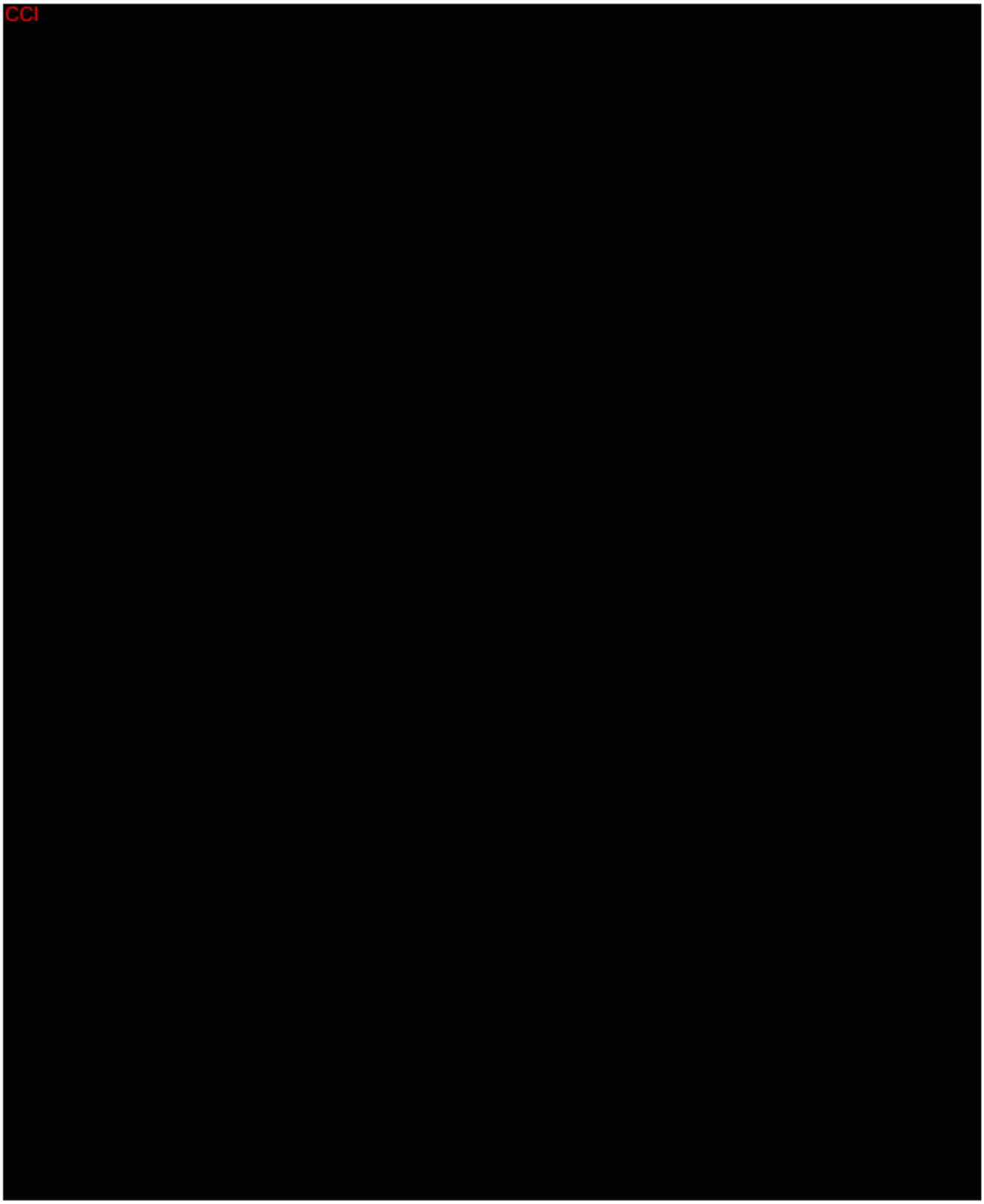
[redacted]



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6.4. Subset Analyses

Descriptive subset analyses may be performed by sex (male, female), ethnicity (Hispanic or Latino, non-Hispanic/non-Latino), and race (White, Black/African American, Asian; other categories may be consolidated into "other" if the numbers of participants are small) for all immunogenicity and safety primary endpoints and some immunogenicity exploratory endpoints.

Further analyses of immunogenicity may be done on influenza or SARS-CoV-2–related endpoints based on baseline HAI titers (<1:10 vs ≥1:10) and baseline SARS-CoV-2 status, and by prior immunization status, respectively.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Descriptive summary statistics for demographic characteristics, including age, sex, race, ethnicity, and BMI, will be generated, by vaccine group and overall (by cohort), based on the safety population and the evaluable immunogenicity population.

6.5.1.2. Medical History

Each reported medical history term will be mapped by SOC and PT according to the current version (at the time of reporting) of MedDRA. The number and percentage of participants with at least 1 diagnosis, overall and at each SOC and PT level, will be summarized for each vaccine group within each cohort for the safety population.

6.5.2. Study Conduct and Participant Disposition

All randomized participants will be included in the disposition summaries. Summaries will be displayed by vaccine group and for the overall study population, by cohort.

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations, completed the follow-up visits, and withdrew from the study, along with the reasons for withdrawal, will be tabulated.

Participants excluded from each analysis population will also be summarized separately, along with the reasons for exclusion, for each vaccine group by cohort.

6.5.2.1. Blood Samples for Assay

For each blood sampling time point, the number and percentage of randomized participants providing blood samples within the protocol-specified time frame, as well as before and after the protocol-specified time frame, will be tabulated, separately, by vaccine group and for the overall study population, by cohort.

6.5.2.2. E-Diaries

The number and percentage of participants with the e-diary transmitted/completed for each day and for all days in the required reporting period will be tabulated for each vaccine group and for the overall study population, by cohort.

6.5.3. Study Vaccination Exposure

The number and percentage of participants randomized and receiving each vaccine will be tabulated for each vaccine group and overall for all randomized participants, by cohort.

A listing of participants showing the randomized vaccine group and the vaccine actually received will be presented.

6.5.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized for the safety population. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated for each vaccine group within each cohort. Prohibited medications and concomitant medications taken to treat any prespecified local or systemic reactogenicity symptoms will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications will be provided.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 7.2.1.

7.2. Interim Analyses and Summaries

Not applicable.

7.2.1. Analysis Timing

Statistical analyses will be carried out when data are available for each cohort as specified below:

- Safety and immunogenicity data through 4 weeks after vaccination after all participants complete 4 weeks of study participation after vaccination (for the respective cohort).
- Safety, immunogenicity, and other data through 6 months after vaccination (for the respective cohort).

Additional analyses may be conducted if required for regulatory purposes after the immunogenicity primary or secondary hypotheses for the respective cohort have been evaluated. The study team will remain blinded through end of the study per Section 6.4 of the protocol, as the analysis prior to the final analysis at end of the study will be performed by a separate unblinded statistical team. The investigator site staff will remain blinded to participants' study arms until the last participant completes the final visit. Laboratory personnel performing the assays will remain blinded until all assays are completed.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.
2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
FDA	Food and Drug Administration (United States)
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
ICD	informed consent document
IRT	interactive response technology
IV	intravenous(ly)
LLOQ	lower limit of quantitation
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NI	noninferiority
NT	neutralizing titer
Omi	Omicron
CCI	[redacted]
PT	preferred term
CCI	[redacted]
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
CCI	[redacted]
WHO	World Health Organization

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	16-May-2024 14:02:47	Final Approval