Protocol C5681001

A PHASE 1/2 RANDOMIZED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MODIFIED RNA COVID-19 VACCINE AND A RECOMBINANT INFLUENZA VACCINE ADMINISTERED AS A SINGLE INJECTION IN HEALTHY ADULTS 50 YEARS OF AGE OR OLDER

Statistical Analysis Plan
(SAP)

Version: 1

Date: 22 Jan 2024

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 22 Jan 2024	Original 18 Dec 2023	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5681001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The estimands corresponding to the primary objectives are described in Table 2.

The safety primary objective evaluations are based on the safety population. In general, completely missing reactogenicity data (ie, all 7 days of collection were missing) will not be imputed. For partially missing reactogenicity data (eg, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days. Missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objective are based on the evaluable immunogenicity population (Section 4). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis. This may be adjusted once additional data on the assay characteristics become available.

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Safety		
To describe the safety and tolerability of the study interventions	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills,	The percentage of participants receiving at least 1 dose of study intervention reporting: • Local reactions for up to 7 days following vaccination

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
	vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	• 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
Immunogenicity		
To describe the immune responses elicited by BNT162b2 (Omi XBB.1.5)/RIV, BNT162b2 (Omi XBB.1.5) + RIV coadministered, and BNT162b2 (Omi XBB.1.5) and RIV administered alone (4 weeks after vaccination)	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFR from before vaccination to 4 weeks after vaccination • Percentage of participants with seroresponse[a] at 4 weeks after vaccination
	HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 4 weeks after vaccination • GMFRs from before vaccination to 4 weeks after vaccination • The percentages of participants achieving HAI seroconversion[b] at 4 weeks after vaccination • The percentages of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by BNT162b2 (Omi XBB.1.5)/RIV, BNT162b2 (Omi XBB.1.5) + RIV coadministered, and BNT162b2 (Omi XBB.1.5) and RIV administered alone (6 months after vaccination)	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 6 months after vaccination • GMFR from before vaccination to 6 months after vaccination • Percentage of participants with seroresponse[a] at 6 months after vaccination

Table 2. List of Primary and Exploratory Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
	HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season	In participants complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 6 months after vaccination • GMFRs from before vaccination to 6 months after vaccination • The percentages of participants achieving HAI seroconversion[b] at 6 months after vaccination • The percentages of participants with HAI titers ≥1:40 before vaccination and at 6 months after vaccination
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern)	SARS-CoV-2–neutralizing titers and/or HAI titers for variants (under monitoring, of interest, and/or of concern) not already specified	
To descriptively compare the immune responses between vaccine groups	SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and HAI titers for the seasonal strains recommended by WHO	GMRs and differences in percentage of participants with seroresponse or seroconversion between vaccine groups
To describe the immune response elicited by RIV using virus microneutralization assays	HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season	

a. 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 is considered seroresponse.

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

2.3. Study Design

This is a Phase 1/2 single-blind (site- and sponsor-unblinded) study to evaluate the safety, tolerability, and immunogenicity of licensed BNT162b2 (Omi XBB.1.5) and RIV administered together as a single injection (referred to as BNT162b2 [Omi XBB.1.5]/RIV) in healthy adults 50 years of age or older.

The safety, tolerability, and immunogenicity of BNT162b2 (Omi XBB.1.5)/RIV administered as a single injection will be compared to BNT162b2 (Omi XBB.1.5) and RIV administered simultaneously as 2 separate injections (coadministered), and to BNT162b2 (Omi XBB.1.5) or RIV when administered alone.

Across Phases 1 and 2, approximately 640 participants in total will be randomized with an equal randomization ratio (1:1:1:1) to each of the following vaccine groups and stratified by age group (50 through 64 years of age and ≥65 years of age):

- **Group 1:** BNT162b2 (Omi XBB.1.5)/RIV (as a single injection) administered in the left deltoid and placebo administered in the right deltoid
- **Group 2:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and RIV administered in the right deltoid
- **Group 3:** BNT162b2 (Omi XBB.1.5) administered in the left deltoid and placebo administered in the right deltoid
- **Group 4:** RIV administered in the left deltoid and placebo administered in the right deltoid

Figure 1. Study Schema

Phase 1 N = 80			
Group 1 BNT162b2/RIV (1.0 mL) + placebo (0.5 mL)	**Group 2 RIV (0.5 mL) + BNT162b2 (0.3 mL)**	**Group 3 BNT162b2 (0.3 mL) + placebo (0.5 mL)**	**Group 4 RIV (0.5 mL) + placebo (0.5 mL)**
Phase 1a (Participants 50 through 64 years of age)			
Sentinel n = 10	Sentinel n = 10	Sentinel n = 10	Sentinel n = 10
Sponsor Safety Data Review[a]			
Phase 1b (Participants ≥65 years of age)			
n = 10	n = 10	n = 10	n = 10
IRC[b]			
Phase 2 N = 560			
Participants ≥50 years of age			
n = 140	n = 140	n = 140	n = 140

a. Progression of the study will occur upon confirmation of an acceptable safety assessment of data accumulated after at least 24 hours and up to 7 days after vaccination.
b. Progression of the study will occur upon confirmation of an acceptable safety assessment of data accumulated after at least 72 hours and up to 7 days after vaccination, once approximately 20 participants in each vaccine group have been vaccinated.

During Phase 1, a total of ~20 participants will be enrolled in each vaccine group. Enrollment of participants in each vaccine group will be controlled such that ~10 participants 50 through 64 years of age (sentinel participants, considered Phase 1a) can be vaccinated in each of the groups on the first day. This will be monitored by the sponsor, who will inform sites to pause enrollment once the target has been reached. Vaccination of the remaining ~40 participants (~10 per vaccine group) will commence no sooner than 24 hours after this safety pause. The participants vaccinated after the safety pause will be ≥65 years of age (considered Phase 1b).

Once ~20 participants per vaccine group have been vaccinated in Phase 1, the IRT system will block any further randomization, pending a review of at least 72 hours of safety data for all participants by the IRC. The outcome of the safety data review will be documented in a memo, which will be circulated to all sites prior to starting enrollment in Phase 2. In Phase 2, 140 participants 50 years of age or older will be enrolled in each of the 4 vaccine groups (Table 3). Participants will be stratified by age group, 50 through 64 years of age and ≥65 years of age.

Table 3. Phase 1/2 Vaccine Group Summary

Vaccine Group Number	Vaccine Group Description	Phase 1[a] (Number of Participants per Vaccine Group)	Phase 2[b] (Number of Participants per Vaccine Group)
1	BNT162b2 (Omi XBB.1.5)/RIV and placebo	20	140
2	BNT162b2 (Omi XBB.1.5) and RIV	20	140
3	BNT162b2 (Omi XBB.1.5) and placebo	20	140
4	RIV and placebo	20	140

a. Phase 1a participants will be 50 through 64 years of age at Visit 1 (Day 1). Phase 1b participants will be ≥65 years of age at Visit 1 (Day 1).
b. Phase 2 participants will be 50 years of age or older at Visit 1 (Day 1).

Prespecified local reaction and systemic event data will be collected in an e-diary during the 7 days, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution), as well as any medication taken during this period to treat any pain symptoms or fever.

Blood samples of approximately 20 mL will be collected from all participants for immunogenicity assessments prior to vaccination and at 4 weeks and 6 months after vaccination.

Following vaccination, AEs will be collected from informed consent signing through Visit 2 (approximately 4 weeks after vaccination), and SAEs will be collected from informed consent signing through Visit 3 (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws will also be collected.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Primary Endpoints

The safety primary endpoints are as follows:

- Local reactions for up to 7 days following vaccination
- 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

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after vaccination, where Day 1 is the day of the vaccination. If a local reaction persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and/or any new reactogenicity reactions that develop to the investigator or the study staff. The investigator will enter this additional information in the CRF.

Presence or Absence

For each local reaction and any local reaction on any day, Table 4 explains 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 the study vaccination.

Table 4. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for the Study Vaccination

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 5. 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 5.

Table 5. Local Reaction Grading Scale

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

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. 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. A Grade 4 reaction will be collected on the CRF.

For each local reaction reported after the study vaccination, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of the vaccination) as follows:

- Maximum severity grade = highest grade (maximum severity) within 7 days after administration (Day 1 through Day 7) among severity grades reported for that local reaction.

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). Resolution is defined as the last day on which the reaction is recorded in the e-diary or CRF. If there is no known date when the reaction ended, then duration will be missing (unknown). Participants with no reported reaction have no duration.

Onset Day

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 participants report change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after vaccination. If a systemic event persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and/or any new reactogenicity events that develop to the investigator or the study staff. The investigator will enter this additional information in the CRF. The derivations for systemic events will be handled similar to the way local reactions are handled for presence of the event, severity level, duration, and onset day (see Section 3.1.1.1).

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6 and recorded in the e-diary or CRF.

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. 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. A Grade 4 systemic event will be collected on the CRF.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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

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 periods 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 reactogenicity e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 7 during analysis. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis.

If a fever of ≥39.0°C (≥102.1°F) 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. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor. Fevers >40.0°C (>104.0°F) will be collected on the CRF.

Table 7. 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)

3.1.1.3. Antipyretic/Analgesic Medication

The use of antipyretic medications to treat pain symptoms or fever associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the 7-day reporting period or longer for ongoing symptoms. For the use of antipyretic medication from Day 1 through Day 7 after vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable:

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

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

3.1.1.4. Adverse Events

AEs will be collected from the time the participant provides informed consent through and including Visit 2 (approximately 4 weeks after vaccination). In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF. AEs will be categorized according to MedDRA terms. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

The safety primary endpoint "AEs from vaccination through 4 weeks after vaccination" and other AE endpoints will be summarized by SOC and PT.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe or life-threatening AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol).

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent through the duration of the study (approximately 6 months after vaccination). SAEs will be categorized according to MedDRA terms. The safety primary endpoint "SAEs from vaccination through 6 months after vaccination" will be summarized, by SOC and PT, at the participant level for each group. Additionally, all SAEs will be presented in the listing.

3.1.2. Immunogenicity Primary Endpoints

- SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers at 4 weeks after vaccination
- HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season at 4 weeks after vaccination

The 4 influenza virus strains recommended by WHO are: A/West Virginia/30/2022 (A/Wisconsin/67/2022 pdm09-like virus) (H1N1), A/Darwin/6/2021 (H3N2), B/Austria/1359417/2021, and B/Phuket/3073/2013.

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the Safety Primary Endpoints section (Section 3.1.1).

3.4. Exploratory Endpoints

- SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and HAI titers against the seasonal strains recommended by WHO for the northern hemisphere 2023-2024 influenza season at 6 months after vaccination
- SARS-CoV-2 neutralizing titers and/or HAI titers for variants (under monitoring, of interest, and/or of concern) not already specified
- HAI titers measured by virus microneutralization assays for the seasonal strains recommended by WHO

3.5. Baseline Variables

Measurements or samples collected prior to the study vaccination are considered the baseline data for the assessments.

3.5.1. Demographics, Medical History, and Physical Examination

Demographic variables will be collected, including age (in years), sex (male or female), race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, unknown, and not reported), ethnicity (Hispanic/Latino or of Spanish origin, non-Hispanic/non-Latino or not of Spanish origin, and not reported), and BMI. In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

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

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

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/analgesic medication are present for any day. If all data are missing for all the items on the e-diary for all 7 days after vaccination, the e-diary will be considered not transmitted.

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Any COVID-19 vaccine from 12 months prior to enrollment until the last visit (Visit 3).
- Licensed or investigational influenza vaccine from 12 months prior to enrollment until the last visit (Visit 3).
- Any vaccinations received from 28 days prior to Visit 1 until the last visit (Visit 3).
- Details of any concomitant medication taken to treat fever or pain (solicited reactogenicity symptoms) as reported in the e-diary will be collected.
- Prohibited medications specified in Section 6.9.1 of the protocol.

Prior and concomitant vaccines and concomitant and prohibited medications will be coded using the WHO Drug Dictionary.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in the table below. Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database, and classifications will be documented per standard operating procedures.

Participant Analysis Set	Description
Screened	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Safety	All participants who receive at least 1 dose of the study intervention.
Evaluable immunogenicity	All eligible assigned participants who receive the study intervention to which they are assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within 27 to 42 days after vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All assigned participants who receive the study intervention and have 1 valid and determinate immunogenicity result after vaccination.

Important protocol deviations will be determined by the clinician. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant 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's medical monitor will identify those participants with important protocol deviations that result in exclusion from analysis populations.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis specified in this study. All statistical analyses will be descriptive.

5.2. General Methods

Other than the IRC review of early Phase 1 safety data before the initiation of Phase 2 enrollment, data from Phase 1 and Phase 2 participants will be combined for the safety and immunogenicity analyses.

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.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

5.2.1. Analysis for Binary Data

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

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

The primary approach to calculate the 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 neutralizing titer category (< median, ≥ median) and age group (50 through 64 years of age, ≥65 years of age). The median of baseline neutralizing titers will be calculated based on the pooled data in the 2 comparator groups.

5.2.2. Analysis for Continuous Data

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

5.2.2.1. Geometric Means

The geometric means 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 log 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 Ratios

Model-Based GMR:

The GMR and the associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes terms for baseline assay results (log scale), age, and comparison group.

Unadjusted GMR:

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results 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.

5.2.2.3. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing 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 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 data points on the left side of the step.

5.3. Methods to Manage Missing Data

In general, completely missing reactogenicity data (ie, all 7 days of collection were missing and no reactogenicity events were reported on the AE CRF) will not be imputed. For partially missing reactogenicity data (eg, 1-6 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 or 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 study vaccination date(s) from the same participant, following the Pfizer standard for handling an incomplete AE start date. A completely missing start date for an AE is not allowed in the data collection.

Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety Primary Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days following vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days following vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will be handled as described in Section 5.3.
- Reporting results: Descriptive statistics for each and any local reaction after vaccination in each arm (left and right deltoid) will be presented by maximum severity and cumulatively across severity levels for each vaccine group. 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. Supplemental Analysis

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population as above and the appropriate analysis methodology and reporting results:

- Duration (days) of each local reaction after vaccination in each arm (left and right deltoid).
- Onset day of each local reaction after vaccination in each arm (left and right deltoid).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after vaccination in each arm (left and right deltoid) will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days following vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will be handled as described in Section 5.3
- Reporting results: Descriptive statistics for each systemic event after vaccination will be presented by maximum severity and cumulatively across severity levels for each vaccine group. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analysis

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after vaccination.
- Onset day of each systemic event after vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group.

The use of antipyretic medication (see Section 3.1.1.3) 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 proportions of participants reporting each systemic event throughout 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.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from vaccination through 4 weeks after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From vaccination through 4 weeks after vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- 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 within 4 weeks after vaccination will be provided for each vaccine group.

6.1.1.3.2. Supplemental Analysis

Related (per investigator assessment) AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and protocol-specified AESIs (defined in Section 8.4.8 of the protocol) will also be summarized by vaccine group.

Symptoms and measurements collected at cardiac evaluation visits for monitoring of potential myocarditis or pericarditis will be presented in a listing, regardless of confirmed diagnosis or not.

In addition to the protocol-specified AESIs, Pfizer also evaluates a dynamic list of AESIs that have specific MedDRA term search strategies during clinical and postauthorization safety data review and signal detection; these include AEs of interest for vaccines in general or due to an association with COVID-19, taking into consideration health authority lists of AESIs for COVID-19 vaccines. These AESIs will also be summarized by vaccine group.

All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be in the listing.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from vaccination through 6 months after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From vaccination through 6 months after vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- 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 Clopper-Pearson 95% CIs of SAEs from vaccination through 6 months after vaccination will be provided for each vaccine group.

6.1.2. Immunogenicity Primary Endpoints

6.1.2.1. SARS-CoV-2 Omicron (XBB.1.5)–Neutralizing Titers

6.1.2.1.1. Main Analysis

- Estimands:
  - GMTs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers before vaccination and at 4 weeks after vaccination.
  - GMFRs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers from before vaccination to 4 weeks after vaccination.
  - Percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) at 4 weeks after vaccination.
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 4 Weeks after vaccination.
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs will be provided for each vaccine group using the statistical methods described in Section 5.2.2.1. The GMFRs and the associated 2-sided 95% CIs will be provided for each vaccine group using the statistical methods described in Section 5.2.2.3. The percentages of participants with seroresponse and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group (Section 5.2.1). 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 is considered seroresponse.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: GMTs before vaccination and at 4 weeks after vaccination, GMFRs from before vaccination to 4 weeks after vaccination, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) at 4 weeks after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group.

Figures:

Empirical RCDCs and bar charts of GMTs and the associated 2-sided 95% CIs will be provided for SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers before and 4 weeks after vaccination for each vaccine group.

6.1.2.1.2. Supportive Analysis

Model-based and unadjusted GMRs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers at 4 weeks after vaccination and the associated 95% CIs will be calculated using the statistical methods described in Section 5.2.2.2 for the following comparative groups:

- BNT162b2 (Omi XBB.1.5)/RIV and placebo (Group 1) vs BNT162b2 (Omi XBB.1.5) and RIV (Group 2).

- BNT162b2 (Omi XBB.1.5)/RIV and placebo (Group 1) vs BNT162b2 (Omi XBB.1.5) and placebo (Group 3).

- BNT162b2 (Omi XBB.1.5) and RIV (Group 2) vs BNT162b2 (Omi XBB.1.5) and placebo (Group 3).

The adjusted and unadjusted difference in percentages of participants with seroresponse at 4 weeks after vaccination and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.1 for the same comparative groups listed above.

6.1.2.2. HAI Titers

6.1.2.2.1. Main Analysis

- Estimands:

  - GMTs of strain-specific HAI titers before vaccination and at 4 weeks after vaccination.

  - GMFRs of strain-specific HAI titers from before vaccination to 4 weeks after vaccination.

- Percentages of participants achieving strain-specific HAI seroconversion at 4 weeks after vaccination.
- Percentages of participants with strain-specific HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination.

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 4 Weeks after vaccination.
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs will be provided for each vaccine group using the statistical methods described in Section 5.2.2.1. The GMFRs and the associated 2-sided 95% CIs will be provided for each vaccine group using the statistical methods described in Section 5.2.2.3. The percentages of participants achieving HAI seroconversion and with HAI titers ≥1:40 and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group (Section 5.2.1). Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest, or an HAI titer of ≥1:10 prior to vaccination with a minimum 4-fold rise at the time point of interest.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: For each influenza virus strain, GMTs before vaccination and at 4 weeks after vaccination, GMFRs from before vaccination to 4 weeks after vaccination, percentages of participants achieving HAI seroconversion at 4 weeks after vaccination, and percentages of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group.

Figures:

Empirical RCDCs and bar charts of GMTs and the associated 2-sided 95% CIs will be provided for each strain-specific HAI titer before and 4 weeks after vaccination for each vaccine group.

6.1.2.2.2. Supportive Analysis

The model-based and unadjusted GMRs of strain-specific HAI titers at 4 weeks after vaccination and the associated 95% CIs will be calculated using the statistical methods described in Section 5.2.2.2 for the following comparative groups:

- BNT162b2 (Omi XBB.1.5)/RIV and placebo (Group 1) vs BNT162b2 (Omi XBB.1.5) and RIV (Group 2).

- BNT162b2 (Omi XBB.1.5)/RIV and placebo (Group 1) vs RIV and placebo (Group 4).
- BNT162b2 (Omi XBB.1.5) and RIV (Group 2) vs RIV and placebo (Group 4).

The adjusted and unadjusted difference in percentages of participants with HAI seroconversion at 4 weeks after vaccination and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.1 for the same comparative groups listed above.

6.2. Secondary Endpoint(s)

Not applicable.

6.3. Other Safety Summaries and Analyses Endpoint(s)

Not applicable.

6.4. Exploratory Endpoints

6.4.1. SARS-CoV-2 Omicron (XBB.1.5)–Neutralizing Titers and HAI Titers

- Estimands:
  - GMTs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers before vaccination and at 6 months after vaccination.
  - GMFRs of SARS-CoV-2 Omicron (XBB.1.5)–neutralizing titers and strain-specific HAI titers from before vaccination to 6 months after vaccination.
  - Percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) and achieving strain-specific HAI seroconversion at 6 months after vaccination.
  - Percentages of participants with strain-specific HAI titers ≥1:40 before vaccination and at 6 months after vaccination.
- Analysis set, analysis methodology, and intercurrent events and missing data are the same as described above for the immunogenicity primary endpoints (Section 6.1.2).
- Reporting results: GMTs before vaccination and at 6 months after vaccination, GMFRs from before vaccination to 6 months after vaccination, percentages of participants with seroresponse to SARS-CoV-2 Omicron (XBB.1.5) at 6 months after vaccination, percentages of participants achieving HAI seroconversion at 6 months after vaccination, and percentages of participants with HAI titers ≥1:40 before vaccination and at 6 months after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. This analysis may be conducted in a selected subset of participants.

6.4.2. SARS-CoV-2 Neutralizing Titers and/or HAI Titers for Emerging Variants

For SARS-CoV-2 neutralizing titers and/or HAI titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified, GMTs, GMFRs, percentages of participants with seroresponse, and percentages of participants with seroconversion or HAI titers ≥1:40 at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above (Section 6.1.2). This analysis may be conducted in a selected subset of participants.

6.4.3. HAI Titers Measured by Virus Microneutralization Assays

For HAI titers measured by virus microneutralization assays, GMTs, GMFRs, and percentages of participants with seroconversion or HAI titers ≥1:40 at the specific time point, along with the associated 95% CIs, will be summarized in the same way as for the immunogenicity primary endpoints described above (Section 6.1.2). This analysis may be conducted in a selected subset of participants.

6.5. Subset Analyses

Subset analyses by age group (50 through 64 years of age and ≥65 years of age) will be performed for the safety and immunogenicity primary endpoints.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

6.6.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination, sex, race, ethnicity, baseline SARS-CoV-2 status, and classification of BMI, will be summarized using descriptive statistics for each vaccine group based on the safety population and the evaluable immunogenicity population.

6.6.1.2. Medical History

Each reported medical history term will be mapped to an 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 by group for the safety population.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the disposition summary. In addition, the numbers and percentages of participants who received the study vaccination, completed the study, and withdrew from the study, along with the reasons for withdrawal, will be tabulated by group (according to the randomized group assignment) and overall. The reasons for withdrawal will be those as specified in the database.

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

6.6.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of the protocol-prespecified time frames will be tabulated separately for each time point, by vaccine group.

6.6.2.3. Transmission of E-Diaries

The number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for the vaccination will be summarized according to the vaccine actually received.

6.6.3. Study Intervention Exposure

The number and percentage of participants randomized and receiving the study interventions will be tabulated, for each vaccine group and overall, for all randomized participants. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall.

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

6.6.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before the study vaccination will be listed. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated by group. Concomitant medications taken to treat fever or pain (solicited reactogenicity symptoms) and prohibited medications will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications will be provided. The safety population will be used.

7. INTERIM ANALYSES

7.1. Introduction

No interim analysis will be conducted for this study. As this is a sponsor–open-label study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development. Statistical analyses will be carried out when the final data for the specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 7.3 below.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analysis Timings

Statistical analyses will be carried out when the following data are available:

- Safety and immunogenicity data through 4 weeks after vaccination.
- Safety and immunogenicity data through 6 months after vaccination.

Additional analyses may be conducted if required for regulatory purposes, to inform product development, and/or for program-level decisions. Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time.

8. REFERENCES

1. Agresti A. Introduction: distributions and inference for categorical data. Chapter 1. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

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
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
BNT162b2 (Omi XBB.1.5)	BNT162b2 Omicron (B.1.1.529 sublineage XBB.1.5)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutinin inhibition assay
ICD	informed consent document
IRC	internal review committee
IRT	interactive response technology
IV	intravenous
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
PT	preferred term
RCDC	reverse cumulative distribution curve
RIV	recombinant influenza vaccine
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
WHO	World Health Organization

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Signed By:	Date(GMT)	Signing Capacity
PPD	23-Jan-2024 14:40:14	Final Approval