Protocol C5261023

A PHASE 1/2, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED VACCINE CANDIDATES AGAINST INFLUENZA AND COVID-19 IN HEALTHY INDIVIDUALS

Statistical Analysis Plan
(SAP)

Version: 1

Date: 06 Nov 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 06 Nov 2024	Original 13 Oct 2024	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C5261023. 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 each primary and exploratory objective are described in Table 2.

The estimands to evaluate the safety objectives are based on the safety population. These estimands estimate vaccine safety after study intervention administration. 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. 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 handled as described in Section 5.3.

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

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability of the study interventions.	• Local reactions (injection site pain, injection site redness, and injection site swelling) • Systemic events (fever, fatigue/tiredness, headache,	In participants receiving study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination

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

Objectives	Endpoints	Estimands
	chills, 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 1 month after vaccination • SAEs from vaccination through 6 months after vaccination
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To describe the immune responses elicited by the study interventions.	• SARS-CoV-2 Omicron KP.2–neutralizing titers	In participants complying with the key protocol criteria (evaluable immunogenicity participants): • GMTs before vaccination and at each time point after vaccination • GMFR from before vaccination to each time point after vaccination • Percentage of participants with seroresponse[a] at each time point after vaccination
	• HAI titers for the 2024-2025 NH seasonal strains recommended by WHO	In participants complying with the key protocol criteria (evaluable immunogenicity participants): • GMTs before vaccination and at each time point after vaccination • GMFRs from before vaccination to each time point after vaccination • Percentages of participants achieving HAI seroconversion[b] at each time point after vaccination • Percentage of participants with HAI titers ≥1:40 before vaccination and at each time point after vaccination
CCI [redacted]		

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

Objectives	Endpoints	Estimands
CCI		

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, observer-blinded (sponsor–open-label) study to evaluate the safety, tolerability, and immunogenicity of vaccine candidates against COVID-19 and influenza as a combined single injection.

The study consists of 2 cohorts; Cohort 1 (Phase 2) will study dose combinations in participants 18 through 64 years of age up to a total mRNA dose of CCI µg, and Cohort 2 (Phase 1) will study dose combinations in participants ≥65 years of age up to a total mRNA dose of CCI µg. Enrollment into Cohorts 1 and 2 will occur independently, and therefore may occur separately or contemporaneously. Enrollment into Cohort 2 is optional and may be initiated at the discretion of the sponsor; commencement of enrollment into Cohort 2 will be communicated to the relevant regulatory agency and ethical review committees in advance.

Enrollment of all vaccine groups in Cohort 1 will occur in parallel, whereas enrollment into Cohort 2 will be stepwise to enable safety data review to occur at total mRNA dose levels ≤CCI µg, prior to escalating to total mRNA dose levels up to CCI µg. Stopping rules will apply for Cohort 2 as detailed in the protocol.

Cohort 1

Approximately CCI participants 18 through 64 years of age will be enrolled into Cohort 1 and randomized equally to receive the study intervention at Visit 1, with up to a total mRNA dose of CCI µg, as shown in Table 3.

Table 3. Cohort 1 Study Intervention Groups

Group	Study Intervention		Total mRNA Dose	Number of Participants
	Right Deltoid	Left Deltoid		
A	BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	[redacted]
B	BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
C	BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
D	tIRV 1 ([redacted] µg)	Placebo	[redacted] µg	
E	TIV	BNT162b2 (Omi KP.2) 30 µg	30 µg	
F	tIRV 2 ([redacted] µg)	Placebo	[redacted] µg	
G	tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
H	tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
I	tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
J	tIRV 3 ([redacted] µg)	Placebo	[redacted] µg	
K	tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
L	tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
M	tIRV 3 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
N	tIRV 3 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	

Cohort 2

Approximately [redacted] participants ≥65 years of age will be enrolled into 2 staggered subcohorts of Cohort 2 (Cohort 2i and 2ii) and randomized equally within each subcohort to receive the study intervention at Visit 1, as shown in Table 4. Cohort 2 enrollment will be split in this way to allow enrollment of lower total mRNA dose groups prior to higher total mRNA dose groups up to a total mRNA dose of [redacted] µg:

- **Cohort 2i**: total mRNA dose ≤[redacted] µg = vaccine groups AA through JJ
- **Cohort 2ii**: total mRNA dose >[redacted] µg to ≤[redacted] µg = vaccine groups KK through MM

Enrollment will commence firstly in Cohort 2i, and the sponsor will review [redacted] of safety data from [redacted] per vaccine group in Cohort 2i prior to permitting enrollment to commence in Cohort 2ii. The sponsor will then review [redacted] of safety data from [redacted] per vaccine group in Cohort 2ii before permitting enrollment of the remaining participants within Cohort 2ii. Stopping rules will apply for Cohort 2 as detailed in the protocol, and the maximum total mRNA dose for any group will be up to [redacted] µg.

Table 4. Cohort 2 Study Intervention Groups

Group	Study Intervention		Total mRNA Dose	Number of Participants
	Right Deltoid	Left Deltoid		
Cohort 2i				
AA	BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	[redacted]
BB	BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
CC	BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
DD	tIRV 1 ([redacted] µg)	Placebo	[redacted] µg	
EE	EIV	BNT162b2 (Omi KP.2) 30 µg	30 µg	
FF	tIRV 2 ([redacted] µg)	Placebo	[redacted] µg	
GG	tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
HH	tIRV 2 ([redacted] µg)/BNT162b2 (Omi KP.2 [redacted] µg	Placebo	[redacted] µg	
II	tIRV 1 ([redacted] µg)/BNT162b2 (Omi KP.2 [redacted] µg	Placebo	[redacted] µg	
JJ	tIRV 3 ([redacted] µg)	Placebo	[redacted] µg	
Cohort 2ii				
KK	tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	[redacted]
LL	tIRV 2 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	
MM	tIRV 3 [redacted] µg)/BNT162b2 (Omi KP.2) [redacted] µg	Placebo	[redacted] µg	

The study includes collection of participant-reported reactogenicity data (local reactions and systemic events) via an e-diary in both cohorts. Prespecified local reaction and systemic event data will be collected after study vaccination (ie, from Day 1, the day of vaccination) through Day 7, or longer for ongoing symptoms, until symptom resolution. Participants are to monitor and record local reactions at the injection site on the right deltoid only within the e-diary. Reported Grade 3 and potential Grade 4 reactogenicity events will be assessed by the investigator or qualified person to determine unscheduled medical visit requirements.

Blood samples of approximately 20 mL will be collected from participants in both cohorts for immunogenicity assessments prior to vaccination, and at 1 month and 6 months after vaccination.

For both cohorts, all AEs will be collected from informed consent signing through 1 month following study intervention administration. AESIs, NDCMCs, and SAEs will be collected from informed consent signing through 6 months after study intervention administration. Protocol-specified AESIs include confirmed diagnoses of myocarditis/pericarditis, menstrual disturbances, [redacted].

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 1 month after vaccination
- SAEs from vaccination through 6 months after vaccination

3.1.1.1. Local Reactions

Participants are to monitor and record local reactions at the injection site on the right deltoid only within the e-diary. Local reactions that occur in the left deltoid will be reported on the AE page. 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 ("Summary of Reactogenicity").

Presence or Absence

For each local reaction and any local reaction on any day, Table 5 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 5. 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 6. 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 6.

Table 6. 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 must 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, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a 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/tiredness, 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 ("Summary of Reactogenicity"). 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 7 and recorded in the e-diary or CRF.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact must 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, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. 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 7. 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
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
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 8 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 must 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), after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). 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 8. Scale for Fever

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
Fever	≥38.0°C to 38.4°C (100.4-101.1°F)	>38.4°C to 38.9°C (101.2-102.0°F)	>38.9°C to 40.0°C (102.1-104.0°F)	>40.0°C (>104.0°F)

3.1.1.3. Adverse Events

AEs will be collected from the time the participant provides informed consent through and including Visit 2 (approximately 1 month 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 1 month 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), NDCMCs, and AESIs (defined in Section 8.4.8 of the protocol).

3.1.1.4. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent through Visit 3 (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.

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described in Section 3.1.1.

3.4. Exploratory Endpoints

- SARS-CoV-2 Omicron KP.2–neutralizing titers at each time point
- HAI titers for the 2024-2025 NH seasonal strains recommended by WHO at each time point

CCI

[redacted]

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 summarized, 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, non-Hispanic/non-Latino, 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.

In this study, a physical examination may be performed prior to vaccination, if clinically indicated. 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 and systemic events 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:

- Last dose of licensed or investigational COVID-19 vaccine, if received, prior to enrollment.

- All licensed or investigational influenza vaccines received within the 3 years prior to enrollment.
- All vaccinations received from 28 days prior to study enrollment until the final visit.
- Prohibited vaccines and medications specified in Section 6.9.1 of the protocol.

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 any study intervention.
Evaluable SARS-CoV-2 immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have at least 1 valid and determinate SARS-CoV-2–neutralizing titer result from the blood sample collected within 27 to 42 days after vaccination, have no reported COVID-19 or new SARS-CoV-2 infection after Visit 1 and up to 1 month after vaccination, and have no other important protocol deviations as determined by the clinician.
Evaluable HAI immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have at least 1 valid and determinate HAI titer result from the blood sample within 27 to 42 days after vaccination, have no reported influenza infection after Visit 1 and up to 1 month after vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive the study intervention and have at least 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 clinician 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

All safety and immunogenicity data will be summarized separately for each cohort.

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 are 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]

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 (GMRs)

Model-Based (Adjusted) 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)

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 (RCDCs)

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 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 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 calculation of 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. 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 will be presented by maximum severity and cumulatively across severity levels 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. 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.
- Onset day of each local reaction after vaccination.

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

Figures:

Bar charts with the proportions of participants for each local reaction reported up to 7 days after vaccination will be plotted for each vaccine group within each cohort. 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 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.

6.1.1.2.2. 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 within each cohort.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days will be plotted for each vaccine group within each cohort. 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 1 month after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From vaccination through 1 month 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 within each cohort.

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), protocol-specified AESIs (defined in Section 8.4.8 of the protocol), and NDCMCs will also be summarized by vaccine group within each cohort.

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 CCI [redacted] These AESIs will also be summarized by vaccine group within each cohort.

All AEs after informed consent and prior to the first vaccination will not be included in the AE summary tables 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 within each cohort.

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 KP.2–Neutralizing Titers

6.4.1.1. Main Analysis

- Estimands:
  - GMTs of SARS-CoV-2 Omicron KP.2–neutralizing titers before vaccination and at each time point after vaccination.
  - GMFRs of SARS-CoV-2 Omicron KP.2–neutralizing titers from before vaccination to each time point after vaccination.
  - Percentages of participants with seroresponse to SARS-CoV-2 Omicron KP.2 at each time point after vaccination.
- Analysis set: Evaluable SARS-CoV-2 immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- 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 each time point after vaccination, GMFRs from before vaccination to each time point after vaccination, and percentages of participants with seroresponse to SARS-CoV-2 Omicron KP.2 at each time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each BNT162b2 recipient group (ie, BNT162b2 standalone, tIRV/BNT162b2, or BNT162b2 + TIV [or EIV in Cohort 2]) within each cohort.

Figures:

Empirical RCDCs and bar charts of GMTs and the associated 2-sided 95% CIs will be provided for SARS-CoV-2 Omicron KP.2–neutralizing titers before vaccination and at each time point after vaccination for each BNT162b2 recipient group within each cohort.

6.4.1.2. Supplemental Analysis

Model-based and unadjusted GMRs of SARS-CoV-2 Omicron KP.2–neutralizing titers at 1 month after vaccination and the associated 95% CIs may be calculated using the statistical methods described in Section 5.2.2.2 for the following comparative groups:

- Each BNT162b2 recipient group to standalone BNT162b2 (Omi KP.2) [CCI] µg group (Group [CCI] in Cohort 1 or Group [CCI] in Cohort 2) within each cohort.

- Each tIRV/BNT162b2 group to BNT162b2 + TIV (or EIV in Cohort 2) group (Group E in Cohort 1 and Group EE in Cohort 2) within each cohort.

The difference in percentages of participants with seroresponse at 1 month after vaccination and the associated 2-sided 95% CIs may be calculated using the statistical methods described in Section 5.2.1 for the same comparative groups listed above.

6.4.2. HAI Titers

6.4.2.1. Main Analysis

- Estimands:

  - GMTs of strain-specific HAI titers before vaccination and at each time point after vaccination.

  - GMFRs of strain-specific HAI titers from before vaccination to each time point after vaccination.

  - Percentages of participants achieving strain-specific HAI seroconversion at each time point after vaccination.

- Percentages of participants with strain-specific HAI titers ≥1:40 before vaccination and at each time point after vaccination.

- Analysis set: Evaluable HAI immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- 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 each time point after vaccination, GMFRs from before vaccination to each time point after vaccination, percentages of participants achieving HAI seroconversion at each time point after vaccination, and percentages of participants with HAI titers ≥1:40 before vaccination and at each time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each influenza vaccine recipient group (ie, tIRV standalone, tIRV/BNT162b2, or BNT162b2 + TIV [or EIV in Cohort 2]) within each cohort.

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 vaccination and at each time point after vaccination for each influenza vaccine recipient group within each cohort.

6.4.2.2. Supplemental Analysis

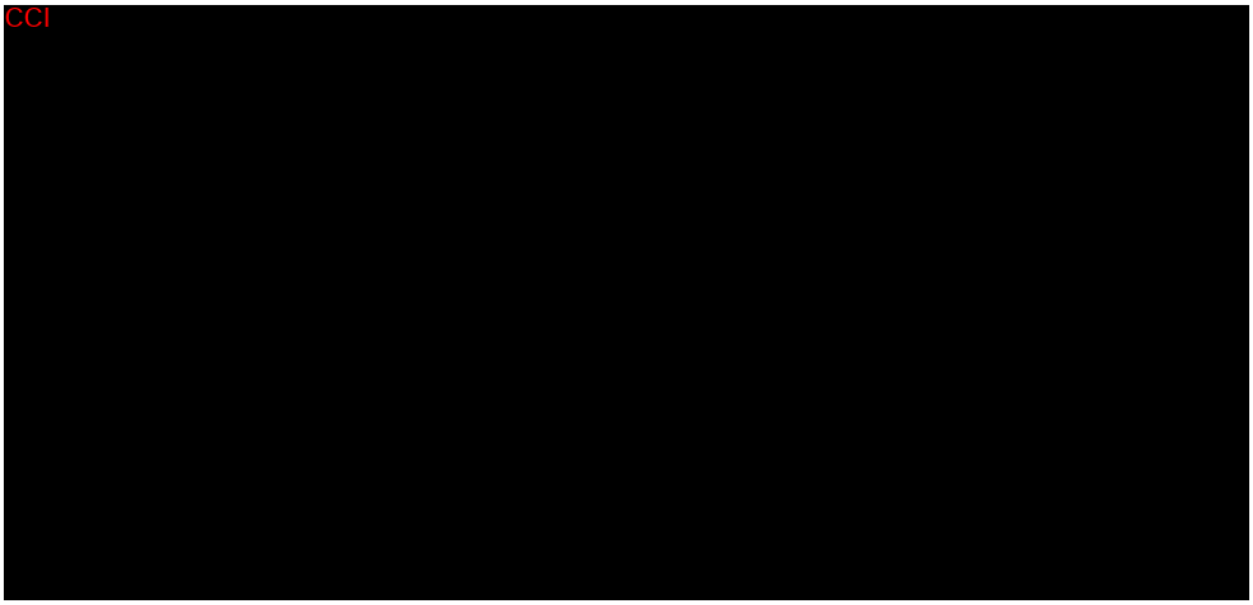
Model-based and unadjusted GMRs of strain-specific HAI titers at 1 month after vaccination and the associated 95% CIs may be calculated using the statistical methods described in Section 5.2.2.2 for the following comparative groups:

- Each influenza vaccine recipient group to standalone [redacted] ([redacted] µg) group (Group F in Cohort 1 or Group FF in Cohort 2) within each cohort.

- Each standalone tIRV group and tIRV/BNT162b2 group to BNT162b2 + TIV (or EIV in Cohort 2) group (Group E in Cohort 1 and Group EE in Cohort 2) within each cohort.

The difference in percentages of participants with seroresponse at 1 month after vaccination and the associated 2-sided 95% CIs may be calculated using the statistical methods described in Section 5.2.1 for the same comparative groups listed above.

CCI



6.5. Subset Analyses

No subset analysis is planned.

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 within each cohort 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 vaccine group within each cohort 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 vaccine group (according to the randomized group assignment) and overall for each cohort. 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 for each cohort.

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 for each cohort.

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 investigational 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, by cohort. 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 investigational vaccine actually received will be presented.

6.6.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized for the safety population. All vaccines received within 28 days before the study vaccination will be listed. Prior COVID-19 and influenza vaccines may be summarized for each vaccine group. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated by group. Prohibited medications will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications as described in Section 3.5.3 will be provided. The safety population will be used.

7. INTERIM ANALYSES

7.1. Introduction

No formal 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 specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 7.3.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analysis Timings

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

- Safety and immunogenicity data through 1 month 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: Categorical data analysis. 2nd ed. Agresti A, ed. Hoboken, NJ: John Wiley & Sons; 2002. p 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	Pfizer-BioNTech COVID-19 vaccine
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EIV	enhanced influenza vaccine
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(ly)
LLOQ	lower limit of quantitation
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NH	northern hemisphere
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

Abbreviation	Term
SOC	system organ class
tIRV	trivalent influenza modRNA vaccine
TIV	trivalent influenza vaccine
WHO	World Health Organization

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	07-Nov-2024 16:33:25	Final Approval