Protocol C4591054 – Substudy A and Substudy B

A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED VACCINE CANDIDATES FOR SARS-CoV-2 NEW VARIANTS IN HEALTHY INDIVIDUALS – SUBSTUDY A AND SUBSTUDY B

Statistical Analysis Plan
(SAP)

Version: 1

Date: 08 Aug 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/Date	Associated Protocol	Rationale	Specific Changes
1 08 Aug 2023	Original 18 Jul 2023	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Substudy A and Substudy B of Study C4591054. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Estimands, and Endpoints

The estimands corresponding to each primary and/or exploratory objective are described in Table 2 for Substudy A and in Table 3 for Substudy B.

The safety primary objective evaluations are based on the safety population. In general, completely missing reactogenicity data (ie, all 7 days of e-diary collection were missing and no reactogenicity events were reported on the AE CRF) will not be imputed. For the partially missing reactogenicity data (ie, 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 (Section 5.3).

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (see Section 4 for definition). 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, Estimands, and Endpoints for Substudy A

Objectives	Estimands	Endpoints
Primary:		
Safety		
To describe the safety and tolerability profile of BNT162b2 (Omi XBB.1.5) 30 µg in mRNA COVID-19 vaccine–experienced participants ≥12 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Immunogenicity		
To describe the immune response to BNT162b2 (Omi XBB.1.5) 30 µg and to BNT162b2 bivalent (WT/Omi BA.4/BA.5)[a] 30 µg in mRNA COVID-19 vaccine–experienced participants ≥12 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT 1 month after vaccination • GMFR from before the study vaccination to 1 month after vaccination • Percentages of participants with seroresponse[b] 1 month after vaccination	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers • SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers
Exploratory:		
To describe the immune response to BNT162b2 (Omi XBB.1.5) 30 µg and to bivalent BNT162b2 (WT/Omi BA.4/BA.5)[a] 30 µg in mRNA COVID-19 vaccine–experienced participants ≥12 years of age.[c]	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[b] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers • SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers
To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases

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

Objectives	Estimands	Endpoints
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[c]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron XBB.1.5 strain in a subset of participants with PBMC samples collected.		

a. The participants ≥12 years of age from Study C4591044 Cohort 2/Cohort 3 who received bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 µg will be used as a historical control for this objective.
b. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
c. Immunogenicity samples from a subset of participants may be tested for this objective.

Table 3. List of Primary and Exploratory Objectives, Estimands, and Endpoints for Substudy B

Objectives	Estimands	Endpoints
Safety:		
Primary		
To describe the safety and tolerability profile of BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants, who were previously SARS-CoV-2 exposed, ≥12 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Table 3. List of Primary and Exploratory Objectives, Estimands, and Endpoints for Substudy B

Objectives	Estimands	Endpoints
Immunogenicity		
To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse[a] rate of the anti-XBB.1.5 immune response elicited by BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants, who were previously SARS-CoV-2 exposed, ≥12 years of age compared to BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the SARS-CoV-2 XBB.1.5–neutralizing titers 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A. • The difference in percentages of participants with seroresponsea to the XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants compared to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers
Exploratory:		
To describe the immune response to BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants, who were previously SARS-CoV-2 exposed, ≥12 years of age, and BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.[b]	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omi XBB.1.5–neutralizing titers
To describe confirmed COVID-19 and severe COVID-19 cases.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[b]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified

Table 3. List of Primary and Exploratory Objectives, Estimands, and Endpoints for Substudy B

Objectives	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron XBB.1.5 strain in a subset of participants with PBMC samples collected.		

a. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. Immunogenicity samples from a subset of participants may be tested for this objective.

2.3. Study Design

Substudy A

Substudy A is an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants 12 through 55 and >55 years of age who have received at least 3 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine received at least 150 days prior to study vaccination (Visit A1/Day 1), will receive a single open-label 30-µg dose of BNT162b2 (Omi XBB.1.5). Approximately 400 participants will be enrolled (see Table 4 and Figure 1). The study duration will be 6 months, with 5 scheduled visits. A reactogenicity e-diary will be used by participants for 7 days from the day of vaccination. The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants in each age group who are ≥18 years of age and consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

Table 4. Substudy A Design

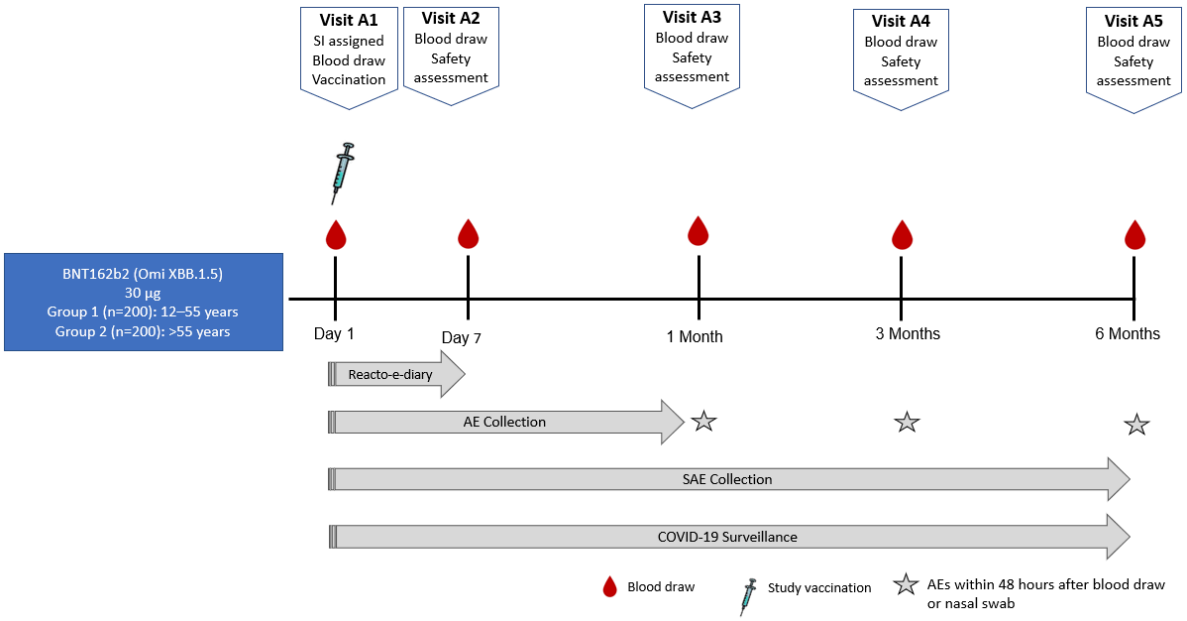
Vaccine: BNT162b2 (Omi XBB.1.5)						
Group	**Participant Age Group**	**Prior Doses[a]**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization/ Blind**
1	12-55 Years[b]	≥3	≥150 Days	30 µg	200	Open-label
2	>55 Years	≥3	≥150 Days	30 µg	200	Open-label

a. Prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine.
b. A maximum of 50 participants aged 12 through 17 years are to be enrolled.

Participants ≥12 years of age from Study C4591044 Cohort 2/Cohort 3 who received bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 µg as a fourth dose will be used as a historical control group.

An EDMC will review all safety data throughout the study.

Figure 1. Schema of Substudy A



Substudy B

Substudy B is an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19, targeting the XBB.1.5 strain. Participants ≥12 years of age who were previously exposed to SARS-CoV-2 and are COVID-19 vaccine–naïve will receive a single 30-µg dose of BNT162b2 (Omi XBB.1.5). Approximately 300 participants will be enrolled (see Table 5 and Figure 2). The study duration will be 6 months, with 5 scheduled visits. A reactogenicity e-diary will be used by participants for 7 days from the day of vaccination. The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 30 participants ≥18 years of age who consent to optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

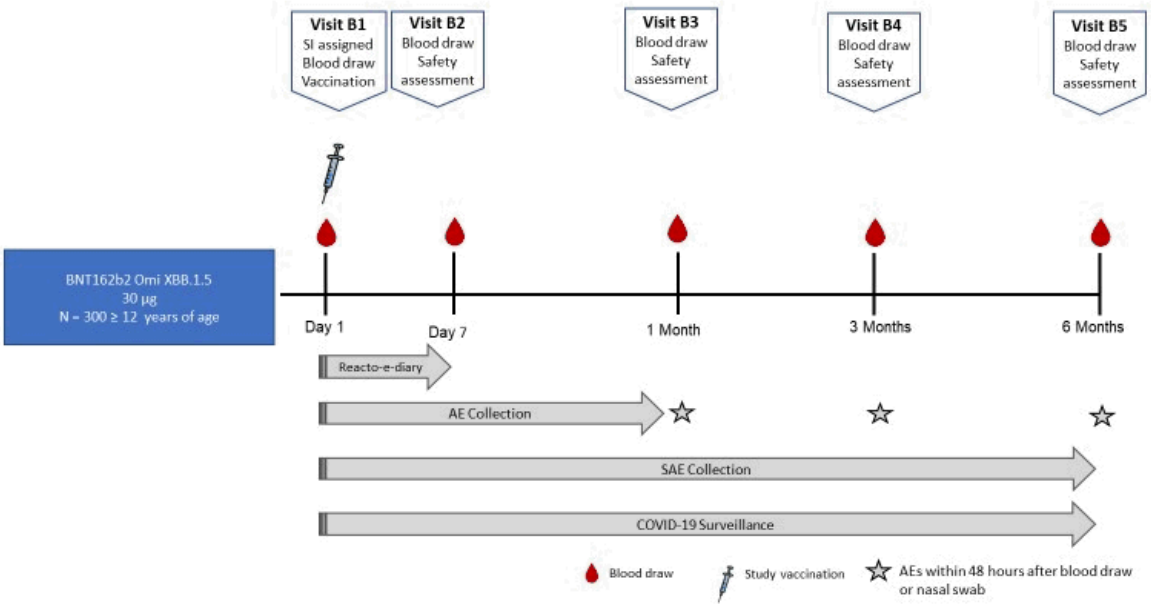
Table 5. Substudy B Design

Vaccine: BNT162b2 (Omi XBB.1.5)						
Group	**Participant Age Group**	**Prior Doses**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization/ Blind**
1	≥12 Years	0		30 µg	300	Open-label

Participants from the C4591054 Substudy A study who received the BNT162b2 (Omi XBB.1.5) 30 µg as a booster dose will be used as a control group to assess the immunogenicity objectives.

An EDMC will review all safety data throughout the study.

Figure 2. Schema of Substudy B



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Primary Endpoints

The safety primary endpoints for Substudy A and Substudy B are as follows:

- Local reactions for up to 7 days after the study vaccination
- Systemic events for up to 7 days after the study vaccination
- AEs from vaccination through 1 month after the study vaccination
- SAEs from vaccination through 6 months after the study 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 the study vaccination, where Day 1 is the day of the study vaccination. The e-diary entries from the participant and unplanned clinical assessments within 7 days after vaccination will be the primary data source for these events. In addition, any AEs recorded on the AE CRF that are considered local reactions within 7 days after vaccination will be consolidated with e-diary data and included in the reactogenicity report. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 6 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 6. 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 7. 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 7.

For events recorded in the AE CRF that are considered local reactions and consolidated with e-diary data, the severity will be based on the AE intensity grade recorded in the CRF.

Table 7. Local Reaction Grading Scale

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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4; therefore, a confirmed Grade 4 reaction should be reported as an AE in the CRF.

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 Pfizer and report it in the designated CRF as Grade 4. A Grade 4 reaction will also be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale.

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 study 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.

If a local reaction is captured in more than 1 data source, eg, e-diary, unplanned assessment, and/or the AE CRF, the highest grade (maximum severity) across all sources will be used in the summary.

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 AE CRF if the reaction lasts 7 days or less, or the day the reaction ends if it persists beyond the end of the reactogenicity e-diary period following the study vaccination (the latter will be collected on the symptom resolution or AE 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 the study vaccination. The e-diary entries from the participant and unplanned clinical assessments within 7 days after vaccination will be the primary data source for these events. In addition, any AEs recorded on the AE CRF that are considered systemic events starting within 7 days after vaccination will be consolidated with e-diary data and included in the reactogenicity report. 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 8 and recorded in the e-diary. For events recorded in the AE CRF that are considered systemic events and consolidated with e-diary data, the severity will be based on the AE intensity grade recorded in the 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 Pfizer and report it in the designated CRF as Grade 4. A Grade 4 systemic event will also be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale,

Table 8. Systemic Event Grading Scale

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

a. Only an investigator or medically qualified person is able to classify an event as Grade 4; therefore, a confirmed Grade 4 event should be reported as an AE in the CRF.

During the 7 days following the study vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: If a test result is positive, the symptoms should be recorded in the potential COVID-19 illness CRFs (with potential COVID-19 illness visit completed) rather than as systemic events in the reactogenicity e-diary (refer to the protocol, Sections 10.7.8.5.7 and 10.7.8.5.8 for Substudy A, and Sections 10.8.8.5.7 and 10.8.8.5.8 for Substudy B).

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

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 9.

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 Pfizer and report it in the designated CRF as fever >40.0°C (>104.0°F). Fevers >40.0°C (>104.0°F) will also be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale. If a fever is reported in the AE CRF within 7 days after vaccination and no temperature was captured in the CRF, the fever will be included in the reactogenicity summary with "unknown" for temperature range.

Table 9. 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)

If a systemic event is captured in more than 1 data source, eg, e-diary, unplanned assessment, and/or the AE CRF, the highest grade (maximum severity) across all sources will be used in the summary.

3.1.1.3. Antipyretic/Analgesic Medication

The use of antipyretic/analgesic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of the study vaccination. For the use of antipyretic/analgesic medication from Day 1 through Day 7 after the study 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/analgesic medication on each day (Day 1 through Day 7)
- Presence (yes or no) of use of antipyretic/analgesic medication on any day (Day 1 through Day 7)
- Duration (first to last day reported) of use of antipyretic/analgesic medication
- Onset day of use of antipyretic/analgesic medication

The use of antipyretic/analgesic 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 or participant's parent(s)/legal guardian provides informed consent through 1 month after the study vaccination. In addition, any AEs occurring up to 48 hours after any subsequent blood draw or nasal swab collection 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 the study vaccination through 1 month after the study 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 AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 10.7.8.4.1 of the protocol for Substudy A and Section 10.8.8.4.1 of the protocol for Substudy B).

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant or participant's parent(s)/legal guardian provides informed consent through approximately 6 months after the study vaccination. SAEs will be categorized according to MedDRA terms. The safety primary endpoint "SAEs from vaccination through 6 months after the study vaccination" will be summarized, by SOC and PT, at the participant level for each group. Additionally, SAEs will be listed.

3.1.2. Immunogenicity Primary Endpoints

Substudy A:

- SARS-CoV-2 Omi XBB.1.5–neutralizing titers at 1 month after the study vaccination
- SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers at 1 month after the study vaccination

Substudy B:

- SARS-CoV-2 Omi XBB.1.5–neutralizing titers at 1 month after the study vaccination

3.2. Exploratory Endpoints

Substudy A:

- SARS-CoV-2 Omi XBB.1.5–neutralizing titers at each time point
- SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers at each time point
- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified at each time point

Substudy B:

- SARS-CoV-2 Omi XBB.1.5–neutralizing titers at each time point
- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified at each time point

3.3. Baseline Variables

For Substudy A and Substudy B, measurements or samples collected prior to the study vaccination are considered the baseline data for the assessments.

3.3.1. Demographics, Medical History, and Physical Examination

The demographic variables will be collected including age (in years), sex (male or female), race (Black or African American, American Indian or Alaskan 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.

3.3.2. 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.

3.3.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Prohibited medications listed in the protocol, Section 10.7.6.9.1 for Substudy A and Section 10.8.6.9.1 for Substudy B, will be recorded in the concomitant medication CRF.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.
- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF (for Substudy A).
- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

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

3.4. Safety Endpoints

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

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.

Population	Description
Screened	All participants who have a signed ICD.
Assigned	All participants who are assigned a randomization number in the IRT system.
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 28 to 42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

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.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. In general, completely missing reactogenicity data (ie, all 7 days of e-diary 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; missing AE dates will be handled according to the Pfizer safety rules (Section 5.3).

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/assigned. Missing serology data will not be imputed.

5. GENERAL METHODOLOGY AND CONVENTIONS

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

Substudy A and Substudy B are both open-label studies. Participants, site personnel, and Pfizer staff are not blinded to participants' assigned study intervention. The timing for statistical analysis is specified in Section 7.3.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

Substudy A

There is no formal hypothesis testing. All statistical analyses will be descriptive.

Substudy B

The immunogenicity primary objective is to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-XBB.1.5 immune response induced by BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants who were previously exposed to SARS-CoV-2 relative to the immune response elicited by BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A. The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(0.67) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omi XBB.1.5–neutralizing titers measured at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants who were previously exposed to SARS-CoV-2;

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omi XBB.1.5–neutralizing titers measured at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.1 \text{ vs } H_1: p_1 - p_2 > -0.1$$

where -10% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to the Omi XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants who were previously exposed to SARS-CoV-2;

  - p_2 is the percentage of participants with seroresponse to the Omi XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy 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.

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

5.1.2. Multiplicity Adjustment

Substudy A

No multiplicity adjustment is needed for Substudy A, as there is no statistical hypothesis.

Substudy B

The 2 hypotheses for the primary objective will be evaluated sequentially using a 1-sided alpha of 0.025. Noninferiority based on GMR will be evaluated first, followed by seroresponse rate difference.

5.2. General Methods

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

5.2.1. Analyses for Binary Endpoints

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 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 (< median, ≥ median). The median of baseline neutralizing titers and median age will be calculated based on the pooled data in the 2 comparator groups.

5.2.2. Analyses for Continuous Endpoints

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

5.2.3. 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 transforms of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

5.2.4. Geometric Mean Ratios

Model-Based GMR:

As the primary approach, the GMR and 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 neutralizing titer, 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.

5.2.5. 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.

5.2.6. 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 complete 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

Unless otherwise specified, the analyses and summaries described in this section apply to both Substudy A and Substudy B.

6.1. Primary Endpoints

6.1.1. Safety Primary Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study 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 the study vaccination in each age subgroup (12-17 years, 18-55 years, >55 years) and overall will be presented by maximum severity and cumulatively across severity levels. 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 appropriate analysis methodology and reporting results:

- Duration (days) of each local reaction after the study vaccination.
- Onset day of each local reaction after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by age subgroup (12-17 years, 18-55 years, >55 years) and overall.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after the study vaccination will be plotted by age subgroup (12-17 years, 18-55 years, >55 years) and overall. 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

- Estimands: 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 after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study 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 the study vaccination in each age subgroup (12-17 years, 18-55 years, >55 years) and overall will be presented by maximum severity and cumulatively across severity levels. 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 the study vaccination.
- Onset day of each systemic event after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by age subgroup (12-17 years, 18-55 years, >55 years) and overall.

The use of antipyretic/analgesic 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/analgesic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days will be plotted for each age subgroup (12-17 years, 18-55 years, >55 years) and overall. 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 the study vaccination through 1 month after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 1 month after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1 and Section 3.1.1.4).
- 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 1 month after the study vaccination will be provided for each age subgroup (12-17 years, 18-55 years, >55 years) and overall.

6.1.1.3.2. Supplemental Analysis

Related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 10.7.8.4.1 of the protocol for Substudy A and Section 10.8.8.4.1 of the protocol for Substudy B) will also be summarized by age subgroup (12-17 years, 18-55 years, >55 years) and overall.

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 the study vaccination through 6 months after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 6 months after the study 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 the study vaccination through 6 months after the study vaccination will be provided for each age subgroup (12-17 years, 18-55 years, >55 years) and overall.

6.1.2. Immunogenicity Primary Endpoints

6.1.2.1. Substudy A

6.1.2.1.1. Main Analysis

- Estimands:
    - GMTs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers at 1 month after vaccination for each age subgroup (12-17 years, 18-55 years, >55 years), overall, and by baseline SARS-CoV-2 infection status

  - GMFRs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers from before the study vaccination to 1 month after vaccination for each age subgroup (12-17 years, 18-55 years, >55 years), overall, and by baseline SARS-CoV-2 infection status

  - Percentages of participants with seroresponse to SARS-CoV-2 Omi XBB.1.5 and SARS-CoV-2 Omi BA.4/BA.5 at 1 month after vaccination for each age subgroup (12-17 years, 18-55 years, >55 years), overall, and by baseline SARS-CoV-2 infection status

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

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at 1 month after vaccination will be provided for each age subgroup using the statistical methods described in Section 5.2.3. The GMFRs and the associated 2-sided 95% CIs from baseline to 1 month after vaccination will be provided for each age subgroup using the statistical methods described in Section 5.2.5. The percentages of participants with seroresponse at 1 month after vaccination and the associated Clopper-Pearson 95% CIs will be provided for each age subgroup (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: For the BNT162b2 (Omi XBB.1.5) group in Substudy A and the historical control of the bivalent BNT162b2 (WT/Omi BA.4/BA.5) group from Study C4591044, GMTs before and 1 month after study vaccination, GMFRs from baseline (before the study vaccination received in this study) to 1 month after vaccination, and percentages of participants with seroresponse to SARS-CoV-2 Omi XBB.1.5 and SARS-CoV-2 Omi BA.4/BA.5 at 1 month after vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup, overall, and by baseline SARS-CoV-2 infection status.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers before and 1 month after study vaccination for each age subgroup. Bar charts of GMTs and the associated 2-sided 95% CIs will be provided for SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers before and 1 month after study vaccination for each age subgroup.

6.1.2.2. Substudy B

6.1.2.2.1. Main Analysis

- Estimands:
    - GMR of the SARS-CoV-2 XBB.1.5–neutralizing titers 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participants to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A
    - The difference in percentages of participants with seroresponse to XBB.1.5 strain at 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given as a single dose to COVID-19 vaccine–naïve participant compared to 1 month after BNT162b2 (Omi XBB.1.5) 30 µg given to vaccine-experienced participants in Substudy A
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs, along with the model-based LS GMTs and associated 2-sided 95% CIs, for each comparison group will be calculated using the linear regression model that includes terms for baseline neutralizing titer, age, and comparison group. Statistical methods are described in Section 5.2.4. The percentages of participants with seroresponse and the associated Clopper-Pearson 95% CIs for each comparison group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median) and age group (<median, ≥ median). Statistical methods are described in Section 5.2.1.
- 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: The LS GMTs and associated 95% CIs for each comparison group, as well as the model-based GMR with their associated 95% CIs, will be summarized. The numbers/percentages of participants with seroresponse for each comparison group and the corresponding 95% CIs, along with the difference in percentages of participants with seroresponse between the 2 comparison groups and the associated 2-sided 95% CIs, will be provided.

6.1.2.2.2. Sensitivity Analysis

To support the interpretation of the primary analysis, the unadjusted GMTs and 95% CIs for each comparison group, as well as the unadjusted GMR and 95% CIs, will be calculated based on the Student t distribution. Statistical methods are described in Section 5.2.3 and Section 5.2.4.

The unadjusted difference in percentages of participants with seroresponse between the 2 comparison groups and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method. Statistical methods are described in Section 5.2.1.

6.2. Exploratory Endpoints

6.2.1. Immunogenicity Exploratory Endpoints

6.2.1.1. Substudy A

- Estimands:
    - GMTs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers at each time point for each age subgroup (12-17 years, 18-55 years, >55 years), overall, and by baseline SARS-CoV-2 infection status
    - GMFRs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers and SARS-CoV-2 Omi BA.4/BA.5–neutralizing titers from before the study vaccination to subsequent time points for each age subgroup (12-17 years, 18-55 years, >55 years), overall, and by baseline SARS-CoV-2 infection status
    - Percentages of participants with seroresponse to SARS-CoV-2 Omi XBB.1.5 and SARS-CoV-2 Omi BA.4/BA.5 at each time point following vaccination for each age subgroup (12-17 years, 18-55 years, >55 years), overall, and by baseline SARS-CoV-2 infection status
- Analysis set, analysis methodology, intercurrent events and missing data, and reporting results are the same as described above for the Substudy A immunogenicity primary endpoint (Section 6.1.2.1). The analysis may be conducted in a selected subset of participants.

6.2.1.2. Substudy B

- Estimands:
    - GMTs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers at each time point for each age subgroup (12-17 years, 18-55 years, >55 years) and overall
    - GMFRs of SARS-CoV-2 Omi XBB.1.5–neutralizing titers from before the study vaccination to subsequent time points for each age subgroup (12-17 years, 18-55 years, >55 years) and overall
    - Percentages of participants with seroresponse to the Omi XBB.1.5 strain at each time point for each age subgroup (12-17 years, 18-55 years, >55 years) and overall
- Analysis set, analysis methodology, and intercurrent events and missing data are the same as described above for the Substudy A immunogenicity primary endpoint (Section 6.1.2.1).
- Reporting results: For COVID-19 vaccine–naïve participants in this substudy and the control group of vaccine-experienced participants from Substudy A, GMTs, GMFRs, and percentages of participants with seroresponse to SARS-CoV-2 Omi XBB.1.5 at each time point, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. This analysis may be conducted in a selected subset of participants. For control group participants from Substudy A, the above analysis may be performed by baseline SARS-CoV-2 infection status if there is a sufficient number of participants without prior SARS-CoV-2 infection.

6.2.2. COVID-19 Cases

Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.

6.2.3. SARS-CoV-2–Neutralizing Titers for Emerging Variants

- Estimands:
    - GMTs of SARS-CoV-2–neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified at specific time points for each age subgroup
    - GMFRs of SARS-CoV-2–neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified from before the study vaccination to subsequent time points for each age subgroup
    - Percentages of participants with seroresponse to SARS-CoV-2–neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified at each time point for each age subgroup

- Analysis set, analysis methodology, and intercurrent events and missing data are the same as described above for the Substudy A immunogenicity primary endpoint (Section 6.1.2.1).

- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2–neutralizing titers for emerging variants from baseline (before the study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each age subgroup and overall.

6.2.4. Cell-Mediated Immune Response

The cell-mediated immune response and additional humoral immune response parameters to the Omicron XBB.1.5 strain will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

6.3. Subset Analyses

Analyses of safety and immunogenicity endpoints by age subgroup (12-17 years, 18-55 years, >55 years) and baseline SARS-CoV-2 infection status (for Substudy A, if there are a sufficient number of participants without prior SARS-CoV-2 infection) are described in Section 6.1 and Section 6.2. Subset analyses by sex will be performed on the primary endpoints.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

6.4.1.1. 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 group based on the safety population and the evaluable immunogenicity population. Timing of the last previous dose of COVID-19 vaccine and the name of all previous doses of COVID-19 vaccinations prior to enrollment will also be summarized for Substudy A.

6.4.1.2. Medical History

Each reported medical history term will be mapped to a 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.

6.4.2. Study Conduct and Participant Disposition

6.4.2.1. Participant Disposition

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

6.4.2.2. Blood Samples for Assay

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

6.4.2.3. 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 study vaccination will be summarized according to the vaccine actually received.

The safety population will be used.

6.4.3. Study Intervention Exposure

6.4.3.1. Vaccination Timing and Administration

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

A listing of participants showing the randomized/assigned vaccine and the vaccine actually received at the study vaccination will be presented.

6.4.3.2. 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. 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.

6.5. Safety Summaries and Analyses

6.5.1. Adverse Events

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in the Safety Primary Endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analyses Timing

Statistical analyses will be carried out when the following data are available for Substudy A and Substudy B:

- Safety and immunogenicity data through Visit 3 (1 month after study vaccination)
- Safety and immunogenicity data through Visit 5 (6 months after study vaccination)

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

8. REFERENCES

1. Collett D. Statistical inference for binary data. Chapter 2. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

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

9. APPENDICES

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 bivalent (WT/Omi BA.4/BA.5)	BNT162b2 wild type and BNT162b2 Omicron(B.1.1.529) sublineage BA.4/BA.5
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HLA	human leukocyte antigen
ICD	informed consent document
IRT	interactive response technology
IV	intravenous
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
N/A	not applicable
Omi	Omicron
PBMC	peripheral blood mononuclear cell
PT	preferred term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SI	study intervention
SOC	system organ class
WHO	World Health Organization
WT	wild-type

Document Approval Record

Document Name:	C4591054 SSA SSB Statistical Analysis Plan V1, 08 Aug 2023
Document Title:	A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLER ABILITY, AND IMMUNOGENICITY OF BNT162B2 RNA-BASED VAC CINE CANDIDATES FOR SARS-COV-2 NEW VARIANTS IN HEALTH Y INDIVIDUALS

Signed By:	Date(GMT)	Signing Capacity
PPD	08-Aug-2023 15:56:23	Final Approval

Protocol C4591054 – Substudy C

A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED VACCINE CANDIDATES FOR SARS-CoV-2 NEW VARIANTS IN HEALTHY INDIVIDUALS – SUBSTUDY C

Statistical Analysis Plan
(SAP)

Version: 2

Date: 23 Aug 2024

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/Date	Associated Protocol	Rationale	Specific Changes
1 12 Apr 2024	1 11 Mar 2024	N/A	N/A
2 23 Aug 2024	2 07 Aug 2024	To be consistent with the changes made in protocol amendment 2	1. Section 2.2: Added objectives, estimands, and endpoints for Cohort 3; removed objectives, estimands, and endpoints for Cohort 1 (only); updated objectives and endpoints for Cohort 1 and Cohort 2 combined; and updated footnotes of Table 2 2. Section 2.3: Added Cohort 3; removed references of a possible second vaccine in Cohort 1; and updated the vaccine name 3. Section 3.1.2 and Section 6.1.2: Updated the immunogenicity primary endpoints for Cohort 1 and Cohort 2 combined and added immunogenicity primary endpoints for Cohort 3 4. Section 3.4 and Section 6.4: Removed the immunogenicity exploratory endpoints of Cohort 1; updated the immunogenicity exploratory endpoints for Cohort 1 and Cohort 2 combined; and added immunogenicity exploratory endpoints for Cohort 3 5. Section 6.4.2: Updated the COVID-19 cases endpoint to include Cohort 3 6. Section 6.4.3: Updated the emerging variants endpoint to include Cohort 3 7. Section 6.4.4: Added cell-mediated immune response and additional humoral immune response endpoints for Cohort 3 and clarified cell-mediated immune response and additional humoral immune response endpoints for Cohort 2 (only) 8. Section 6.1.1.3.2: Updated “immediate AEs” to “immediate events” 9. Section 7.3: Updated to clarify that analyses would be done for Cohort 1 and Cohort 2 combined and Cohort 3

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Substudy C of Study C4591054. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary and/or exploratory objective 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 e-diary collection were missing and no reactogenicity events were reported on the participant-reported reactogenicity CRF) will not be imputed. For the partially missing reactogenicity data (ie, 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 (Section 5.3).

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (see Section 4 for definition). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedule 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, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
Safety		
Cohort 1 and Cohort 2 combined: To describe the safety and tolerability profile of BNT162b2 (Omi JN.1) 30 µg in participants ≥12 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Cohort 3: To describe the safety and tolerability profile of BNT162b2 (Omi KP.2) 30 µg in participants ≥18 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

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

Objectives	Estimands	Endpoints
	• AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• AEs • SAEs
Immunogenicity		
Cohort 1 and Cohort 2 combined: To describe the immune response to BNT162b2 (Omi JN.1) 30 µg and BNT162b2 (Omi XBB.1.5)[a] 30 µg in participants ≥12 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT 1 month after vaccination • GMFR from before the study vaccination to 1 month after vaccination • Percentages of participants with seroresponse[b] 1 month after vaccination	• SARS-CoV-2 Omi JN.1–neutralizing titers • SARS-CoV-2 Omi XBB.1.5–neutralizing titers
Cohort 3: To describe the immune response to BNT162b2 (Omi KP.2) 30 µg and BNT162b2 (Omi JN.1)[c] 30 µg in participants ≥18 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT 1 month after vaccination • GMFR from before the study vaccination to 1 month after vaccination • Percentages of participants with seroresponse[b] 1 month after vaccination	• SARS-CoV-2 Omi KP.2–neutralizing titers • SARS-CoV-2 Omi JN.1–neutralizing titers
Exploratory:	**Exploratory:**	**Exploratory:**
Cohort 1 and Cohort 2 combined: To describe the immune response to BNT162b2 Omi (JN.1)[d] 30 µg and BNT162b2 (Omi XBB.1.5)[a] 30 µg in participants ≥12 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[b] at each time point following vaccination for each variant-specific neutralizing titer	• SARS-CoV-2 Omi JN.1–neutralizing titers • SARS-CoV-2 Omi XBB.1.5–neutralizing titers
Cohort 3: To describe the immune response to BNT162b2 (Omi KP.2)[d] 30 µg and BNT162b2 (Omi JN.1)[c] 30 µg in participants ≥18 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point • GMFR from before the study vaccination to each subsequent time point • Percentages of participants with seroresponse[b] at each time point following vaccination for each variant-specific neutralizing titer	• SARS-CoV-2 Omi KP.2–neutralizing titers • SARS-CoV-2 Omi JN.1–neutralizing titers

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

Objectives	Estimands	Endpoints
Cohort 1 and Cohort 2 combined: To describe confirmed COVID-19 and severe COVID-19 cases.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 3: To describe confirmed COVID-19 and severe COVID-19 cases.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1 and Cohort 2 combined: To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[d]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified
Cohort 3: To describe the immune response to emerging variants (under monitoring, of interest, and/or of concern).[d]		• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron JN.1 strain in a subset of participants ≥18 years of age with PBMC samples collected.		
Cohort 3: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the Omicron KP.2 strain in a subset of participants with PBMC samples collected.		

a. The participants from Substudy A will be used as a historical control for this objective, for the matched time points.
b. 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.
c. The participants from Substudy C Cohort 1 and Cohort 2 combined will be used as a historical control.
d. Immunogenicity samples from a subset of participants may be tested for this objective.

2.3. Study Design

This is a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of 2 BNT162b2-based vaccines each targeting a predominant circulating variant of SARS-CoV-2. The substudy will be divided into 3 cohorts.

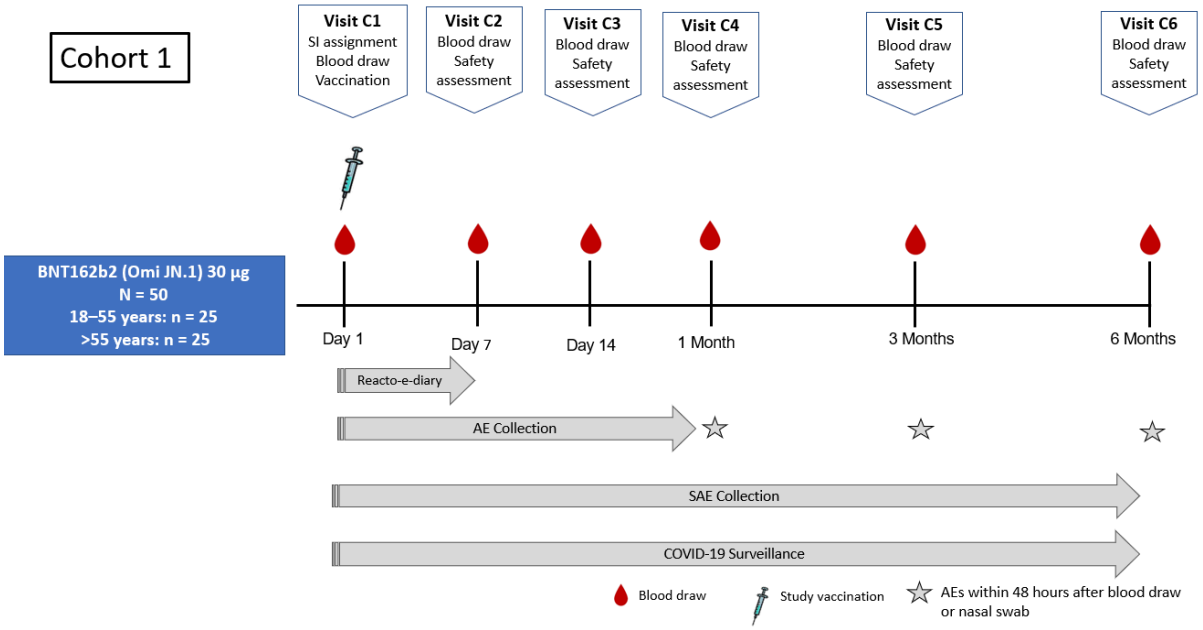
Cohort 1 will enroll approximately 50 participants 18 years of age and older (approximately 25 participants each in the 18- through 55-year and >55-year age groups), who will receive a single 30-µg dose of BNT162b2 (Omi JN.1). The study duration will be approximately 6 months, with 6 scheduled visits. Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity.

Participants from Study C4591054 – Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group for immunogenicity, for the matched time points.

Table 3. Substudy C Design: Cohort 1

Open-Label				
Group	**Study Intervention**	**Study Dose**	**Participant Age Groups**	**Number of Participants**
1	BNT162b2 (Omi JN.1)	30 µg	18-55 Years	25
			>55 Years	25

Figure 1. Schema of Substudy C: Cohort 1



Cohort 2 will enroll participants ≥12 years of age who will receive a single open-label 30-µg dose of BNT162b2 (Omi JN.1). Enrollment into Cohort 2 will begin once Cohort 1 has completed enrollment. Approximately 150 participants will be enrolled into Cohort 2, resulting in a total of 200 participants receiving BNT162b2 (Omi JN.1) (including the 50 participants from Cohort 1). The study duration will be approximately 6 months, with 5 scheduled visits (no 2-week visit). Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A group of approximately 30 participants each in the 18- through 55-year and >55-year age groups who consent to the collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

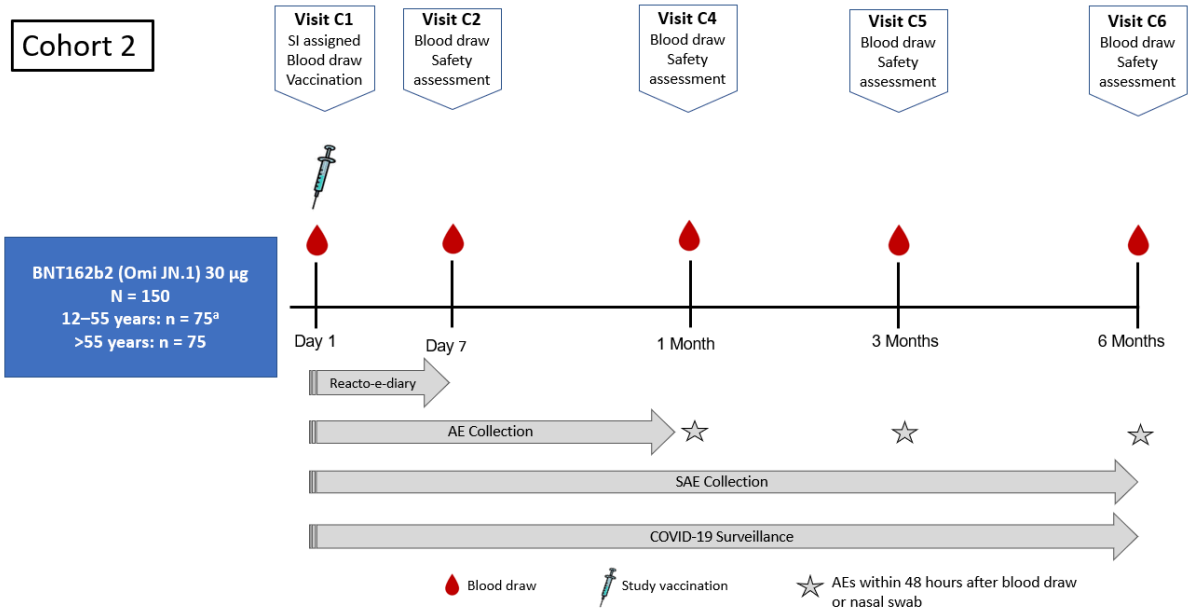
For both cohorts, participants from Study C4591054 – Substudy A who received BNT162b2 (Omi XBB.1.5) 30 µg will be used as a control group for immunogenicity assessment (for the matched time points).

Table 4. Substudy C Design: Cohort 2

Open-Label				
Group	**Study Intervention**	**Study Dose**	**Participant Age Groups**	**Number of Participants**
1	BNT162b2 (Omi JN.1)	30 µg	12-55 Years	75[a]
			>55 Years	75

a. A maximum of 20 participants 12 through 17 years of age will be enrolled. If fewer than 20 participants are enrolled in this age group, the difference will be added to the number of participants enrolled in the 18-through 55-year age group.

Figure 2. Schema of Substudy C: Cohort 2



a. A maximum of 20 participants 12 through 17 years of age will be enrolled. If fewer than 20 participants are enrolled in this age group, the difference will be added to the number of participants enrolled in the 18- through 55-year age group.

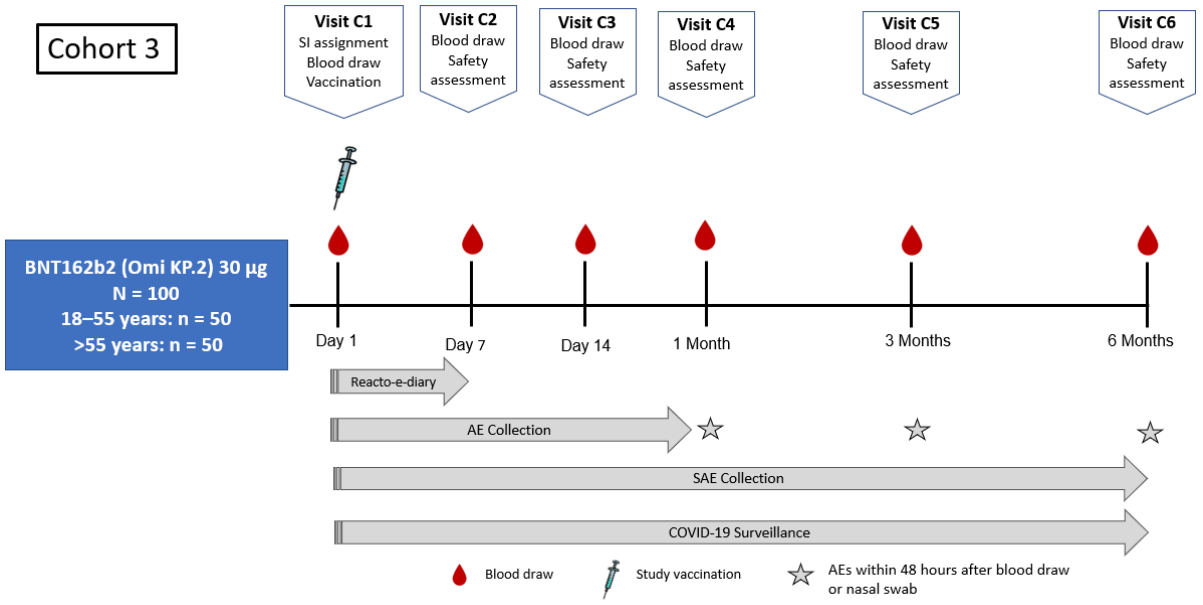
Cohort 3 will enroll participants ≥18 years of age who will receive a single open-label, 30-µg dose of BNT162b2 (Omi KP.2), which targets the SARS-CoV-2 variant Omicron KP.2. Approximately 100 participants will be enrolled. The study duration will be approximately 6 months, with 6 scheduled visits. Reactogenicity e-diaries will be used to collect prespecified local reaction and systemic event data during the 7-day collection period, or longer for ongoing symptoms, after study intervention administration (ie, from Day 1, the day of vaccination, until symptom resolution). The active collection period for AEs will be through approximately 1 month after vaccination and for SAEs through approximately 6 months after vaccination. COVID-19 surveillance will be conducted throughout the study. Blood samples will be taken at each visit for all participants for assessment of immunogenicity. A subset of approximately 20 participants each in the 18- through 55-year and >55-year age groups who consent to collection of optional additional blood samples will comprise the PBMC subset for exploratory evaluation of B- and T-cell responses and HLA typing.

Participants from Cohort 1 and Cohort 2 combined who received BNT162b2 (Omi JN.1) 30 µg will be used as a control group for immunogenicity assessment of BNT162b2 (Omi KP.2).

Table 5. Substudy C Design: Cohort 3

Open-Label				
Group	**Study Intervention**	**Study Dose**	**Participant Age Group**	**Number of Participants**
1	BNT162b2 (Omi KP.2)	30 µg	18-55 Years	50
			>55 Years	50

Figure 3. Schema of Substudy C: Cohort 3



All cohorts will enroll participants who are either COVID-19 vaccine–naïve or experienced. Those who have received prior COVID-19 vaccine(s) must have received the most recent dose at least 150 days prior to study vaccination (Visit C1/Day 1).

An EDMC will review all safety data throughout the study.

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 (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after the study vaccination.
- AEs from the study vaccination through 1 month after the study vaccination.
- SAEs from the study vaccination through 6 months after the study vaccination.

3.1.1.1. Local Reactions

The local reactions, including redness, swelling, and pain at the injection site, are reported in the e-diary and/or CRF from Day 1 through Day 7 after the study vaccination, where Day 1 is the day of vaccination. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 6 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 6. Derived Variables for the Presence of Each and Any Local Reaction Within 7 Days After 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 7. 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 7.

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, 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 local reaction, the investigator must immediately notify Pfizer. A Grade 4 reaction will be collected on the CRF.

Table 7. Local Reaction Grading Scale

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

a. Only an investigator or medically qualified person is able to classify a reaction as Grade 4.

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 study 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.

If a local reaction is captured in more than 1 data source, eg, the e-diary and the participant-reported reactogenicity CRF at unplanned assessments, the highest grade (maximum severity) across all sources will be used in the summary.

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. For a reaction collected in multiple sources, the earliest start date and the latest end date will be used in calculating duration. 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 a reaction of any severity after vaccination. Change in severity during the event does not impact the originally determined onset day. For example, for the onset day of each local reaction, if participants report a change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

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

3.1.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary and/or CRF are fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after the study vaccination. 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 8.

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

Table 8. Systemic Event Grading Scale

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

Table 8. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

a. Only an investigator or medically qualified person is able to classify an event as Grade 4.

During the 7 days following the study vaccination, potential COVID-19 symptoms that overlap with prespecified systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed. If a test result is positive, the symptoms should be recorded in the potential COVID-19 illness CRFs (with potential COVID-19 illness visit completed) rather than as systemic events in the reactogenicity e-diary (refer to the protocol, Sections 10.9.8.5.8 and 10.9.8.5.9).

Temperature will be collected in the reactogenicity e-diary for 7 days, or longer following vaccination (where Day 1 is the day of vaccination). 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 for reporting. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 9.

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), 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 fever >40.0°C (>104.0°F), the investigator must immediately notify Pfizer. Fevers >40.0°C (>104.0°F) will be collected on the CRF.

Table 9. 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)

Table 9. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>40.0°C (>104.0°F)

3.1.1.3. Adverse Events

AEs will be collected from the time the participant or participant's parent(s)/legal guardian(s) provides informed consent through 1 month after the study vaccination. In addition, any AEs occurring up to 48 hours after any subsequent blood draw or nasal swab collection 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 the study vaccination through 1 month after the study 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 AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 10.9.8.4.1 of the protocol).

3.1.1.4. Serious Adverse Events

SAEs will be collected from the time the participant or participant's parent(s)/legal guardian(s) provides informed consent through approximately 6 months after the study vaccination. SAEs will be categorized according to MedDRA terms. The safety primary endpoint "SAEs from the study vaccination through 6 months after the study vaccination" will be summarized, by SOC and PT, at the participant level for each group. Additionally, SAEs will be listed.

3.1.2. Immunogenicity Primary Endpoints

Cohort 1 and Cohort 2 combined:

- SARS-CoV-2 Omi JN.1–neutralizing titers
- SARS-CoV-2 Omi XBB.1.5–neutralizing titers

Cohort 3:

- SARS-CoV-2 Omi KP.2–neutralizing titers
- SARS-CoV-2 Omi JN.1–neutralizing titers

3.2. Secondary Endpoints

Not applicable.

3.3. Other Safety Endpoints

Not applicable.

3.4. Exploratory Endpoints

Cohort 1 and Cohort 2 combined:

- SARS-CoV-2 Omi JN.1–neutralizing titers
- SARS-CoV-2 Omi XBB.1.5–neutralizing titers
- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified

Cohort 3:

- SARS-CoV-2 Omi KP.2–neutralizing titers
- SARS-CoV-2 Omi JN.1–neutralizing titers
- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern) not already specified

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

The demographic variables will be collected, including age (in years), sex (male or female), race (Black or African American, American Indian or Alaskan 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:

- Prohibited medications listed in the protocol, Section 10.9.6.9.1, will be recorded in the concomitant medication CRF.
- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.
- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.
- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

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

3.6. Safety Endpoints

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

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.

Population	Description
Screened	All participants who have a signed ICD.
Randomized/Assigned	All participants who are assigned a randomization number in the IRT system.
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 28 to 42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

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.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. In general, completely missing reactogenicity data (ie, all 7 days of e-diary collection were missing and no reactogenicity events were reported on the participant-reported reactogenicity CRF) will not be imputed. For partially missing reactogenicity data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days. Missing AE dates will be handled according to the Pfizer safety rules (Section 5.3).

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/assigned. Missing serology data will not be imputed.

5. GENERAL METHODOLOGY AND CONVENTIONS

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

This is an open-label study. Participants, site personnel, and Pfizer staff are not blinded to the participants' assigned study intervention. The timing for statistical analysis is specified in Section 7.3.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

There is no statistical hypothesis testing planned for this study. All statistical analyses are descriptive and for estimation purposes.

5.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed, as there is no statistical hypothesis.

5.2. General Methods

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

5.2.1. Analyses for Binary Endpoints

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]

5.2.2. Analyses for Continuous Endpoints

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

5.2.3. 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 transforms of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

5.2.4. 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.

5.2.5. 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) will not be imputed. For partially missing reactogenicity data (ie, 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 complete 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

The analyses specified in this section apply to Cohort 1 and Cohort 2 combined and Cohort 3.

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 after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study 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 the study vaccination in each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall will be presented by maximum severity and cumulatively across severity levels. 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 the study vaccination.
- Onset day of each local reaction after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after the study vaccination will be plotted by age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall. 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 after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study 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 the study vaccination in each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall will be presented by maximum severity and cumulatively across severity levels. 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 the assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration (days) of each systemic event after the study vaccination.
- Onset day of each systemic event after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days will be plotted for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall. 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 the study vaccination through 1 month after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 1 month after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1 and Section 3.1.1.3).
- 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 1 month after the study vaccination will be provided for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

6.1.1.3.2. Supplemental Analysis

Related AEs, severe AEs, immediate events (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 10.9.8.4.1 of the protocol) will also be summarized by age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

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 the study vaccination through 6 months after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 6 months after the study 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 the study vaccination through 6 months after the study vaccination will be provided for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

6.1.2. Immunogenicity Primary Endpoints

6.1.2.1. Cohort 1 and Cohort 2 Combined

6.1.2.1.1. Main Analysis

- Estimands:
  - GMTs of SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers at 1 month after vaccination for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.
  - GMFRs of SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers from before the study vaccination to 1 month after the study vaccination for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

  - Percentages of participants with seroresponse to SARS-CoV-2 Omi JN.1 and SARS-CoV-2 Omi XBB.1.5 at 1 month after vaccination for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

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

- Analysis time points: 1 Month after vaccination, from before the study vaccination to 1 month after the study vaccination (for GMFRs only).

- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at 1 month after the study vaccination will be provided using the statistical methods described in Section 5.2.3. The GMFRs and the associated 2-sided 95% CIs from before the study vaccination to 1 month after the study vaccination will be provided using the statistical methods described in Section 5.2.4. The percentages of participants with seroresponse at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided (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: For the BNT162b2 (Omi JN.1) group in Substudy C Cohort 1 and Cohort 2 combined and the historical control of the BNT162b2 (Omi XBB.1.5) group from Substudy A, respectively, GMTs before and 1 month after the study vaccination, GMFRs from before the study vaccination to 1 month after vaccination, and percentages of participants with seroresponse to SARS-CoV-2 Omi JN.1 and SARS-CoV-2 Omi XBB.1.5 at 1 month after vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. The above analysis may be performed by baseline SARS-CoV-2 infection status if there is a sufficient number of participants without prior SARS-CoV-2 infection. Additionally, the above analysis may be performed by prior COVID-19 vaccine history at baseline (naive or experienced) if there is a sufficient number of participants in both of these categories.

Figures:

Empirical RCDCs may be provided for SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers before and 1 month after the study vaccination for each age subgroup. Bar charts of GMTs and the associated 2-sided 95% CIs will be provided for SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers before and 1 month after the study vaccination for each age subgroup.

6.1.2.2. Cohort 3

6.1.2.2.1. Main Analysis

- Estimands:
  - GMTs of SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers at 1 month after vaccination for each age subgroup (18-55 years, >55 years) and overall.
  - GMFRs of SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers from before the study vaccination to 1 month after the study vaccination for each age subgroup (18-55 years, >55 years) and overall.
  - Percentages of participants with seroresponse to SARS-CoV-2 Omi KP.2 and SARS-CoV-2 Omi JN.1 at 1 month after vaccination for each age subgroup (18-55 years, >55 years) and overall.
- Analysis sets: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: 1 Month after vaccination, from before the study vaccination to 1 month after the study vaccination (for GMFRs only).
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at 1 month after the study vaccination will be provided using the statistical methods described in Section 5.2.3. The GMFRs and the associated 2-sided 95% CIs from before the study vaccination to 1 month after the study vaccination will be provided using the statistical methods described in Section 5.2.4. The percentages of participants with seroresponse at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided (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: For the BNT162b2 (Omi KP.2) group in Substudy C Cohort 3 and the historical control of the BNT162b2 (Omi JN.1) group from Substudy C Cohort 1 and Cohort 2 combined, respectively, GMTs before and 1 month after the study vaccination, GMFRs from before the study vaccination to 1 month after vaccination, and percentages of participants with seroresponse to SARS-CoV-2 Omi KP.2 and SARS-CoV-2 Omi JN.1 at 1 month after vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. The above analysis may be performed by baseline SARS-CoV-2 infection status if there is a sufficient number of participants without prior SARS-CoV-2 infection. Additionally, the above analysis may be performed by prior

COVID-19 vaccine history at baseline (naive or experienced) if there is a sufficient number of participants in both of these categories.

Figures:

Empirical RCDCs may be provided for SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers before and 1 month after the study vaccination for each age subgroup. Bar charts of GMTs and the associated 2-sided 95% CIs will be provided for SARS-CoV-2 KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers before and 1 month after the study vaccination for each age subgroup.

6.2. Secondary Endpoints

Not applicable.

6.3. Other Safety Summaries and Analyses Endpoints

Not applicable.

6.4. Exploratory Endpoints

6.4.1. Immunogenicity Exploratory Endpoints

6.4.1.1. Cohort 1 and Cohort 2 Combined

- Estimands:
    - GMTs of SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers at each time point for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.
    - GMFRs of SARS-CoV-2 Omi JN.1–neutralizing titers and SARS-CoV-2 Omi XBB.1.5–neutralizing titers from before the study vaccination to each subsequent time point for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.
    - Percentages of participants with seroresponse to SARS-CoV-2 Omi JN.1 and SARS-CoV-2 Omi XBB.1.5 at each time point following the study vaccination for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.
- Analysis set, analysis methodology, intercurrent events and missing data, and reporting results are the same as described above for the immunogenicity primary endpoint (Section 6.1.2.1). The analysis may be conducted in a selected subset of participants.

6.4.1.2. Cohort 3

- Estimands:
    - GMTs of SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers at each time point for each age subgroup (18-55 years, >55 years) and overall.
    - GMFRs of SARS-CoV-2 Omi KP.2–neutralizing titers and SARS-CoV-2 Omi JN.1–neutralizing titers from before the study vaccination to each subsequent time point for each age subgroup (18-55 years, >55 years) and overall.
    - Percentages of participants with seroresponse to SARS-CoV-2 Omi KP.2 and SARS-CoV-2 Omi JN.1 at each time point following the study vaccination for each age subgroup (18-55 years, >55 years) and overall.
- Analysis set, analysis methodology, intercurrent events and missing data, and reporting results are the same as described above for the immunogenicity primary endpoint (Section 6.1.2.2). The analysis may be conducted in a selected subset of participants.

6.4.2. COVID-19 Cases

6.4.2.1. Cohort 1 and Cohort 2 combined, Cohort 3

Confirmed COVID-19 cases, confirmed severe COVID-19 cases, and strain sequencing of the COVID-19 cases will be summarized.

6.4.3. SARS-CoV-2–Neutralizing Titers for Emerging Variants

6.4.3.1. Cohort 1 and Cohort 2 combined, Cohort 3

- Estimands:
    - GMTs of SARS-CoV-2–neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified at specific time points for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years).
    - GMFRs of SARS-CoV-2–neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified from before the study vaccination to each subsequent time point for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years).
    - Percentages of participants with seroresponse to SARS-CoV-2–neutralizing titers for emerging variants (under monitoring, of interest, and/or of concern) not already specified at each time point for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years).

- Analysis set, analysis methodology, and intercurrent events and missing data are the same as described above for the immunogenicity primary endpoint (Section 6.1.2.1).

- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2–neutralizing titers for emerging variants from before the study vaccination to each subsequent time point after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each age subgroup and overall. The percentages of participants with seroresponse at each time point after the study vaccination, and the associated Clopper-Pearson 95% CIs, will be provided for each age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) and overall.

6.4.4. Cell-Mediated Immune Response

Cohort 2:

The cell-mediated immune response and additional humoral immune response parameters to the SARS-CoV-2 (Omi JN.1) strain will be summarized at each time point for the subset of participants with PBMC samples collected in each age group.

Cohort 3:

The cell-mediated immune response and additional humoral immune response parameters to the SARS-CoV-2 (Omi KP.2) strain will be summarized at each time point for the subset of participants with PBMC samples collected in each age group.

6.5. Subset Analyses

Analyses of safety and immunogenicity endpoints by age subgroup (12-17 years [for Cohort 2 only], 18-55 years, >55 years) are described in Section 6.1. Subset analyses by baseline SARS-CoV-2 infection status (if there is a sufficient number of participants without prior SARS-CoV-2 infection), prior COVID-19 vaccine history at baseline (if there is a sufficient number of participants in both of these categories), and subset analyses by sex may be performed on the 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 group based on the safety population and the evaluable immunogenicity population. Timing of the last previous dose of COVID-19 vaccine and the name of all previous doses of COVID-19 vaccinations prior to enrollment will also be summarized for the vaccine-experienced participants.

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/assigned 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 randomized/assigned 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 group.

6.6.2.2. Blood Samples for Assay

The number and percentage of randomized/assigned participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for each time point, by 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 study vaccination will be summarized according to the vaccine actually received.

The safety population will be used.

6.6.3. Study Intervention Exposure

6.6.3.1. Vaccination Timing and Administration

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

A listing of participants showing the randomized/assigned vaccine and the vaccine actually received at the study vaccination will be presented.

6.6.3.2. Prior/Concomitant Vaccinations and Concomitant Medications

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. 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.

6.7. Safety Summaries and Analyses

6.7.1. Adverse Events

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in the Safety Primary Endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted, as there is no formal hypothesis testing. As this is a sponsor-open 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. Analyses Timing

Statistical analyses will be carried out when the following data are available, for Cohort 1 and Cohort 2 combined and for Cohort 3:

- Safety and immunogenicity data through Visit C4 (1 month after the study vaccination).
- Safety and immunogenicity data through Visit C6 (6 months after the study 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. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
GMFR	geometric mean fold rise
GMT	geometric mean titer
HLA	human leukocyte antigen
ICD	informed consent document
IRT	interactive response technology
IV	intravenous
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
N/A	not applicable
Omi	Omicron
PBMC	peripheral blood mononuclear cell
PT	preferred term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SI	study intervention
SOC	system organ class
WHO	World Health Organization

Document Approval Record

Document Name:	C4591054 Substudy C Statistical Analysis Plan V2 Clean copy, 23Aug 2024
Document Title:	A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED VACCINE CANDIDATES FOR SARS-CoV-2 NEW VARIANTS IN HEALTHY INDIVIDUALS – SUBSTUDY C

Signed By:	Date(GMT)	Signing Capacity
PPD	23-Aug-2024 18:23:44	Final Approval