Protocol C4591031 – Substudy C

A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 – SUBSTUDY C

Statistical Analysis Plan
(SAP)

Version: 4

Date: 25 Sep 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment/ Date	Rationale	Specific Changes
1/ 15 Dec 2021	3/ 28 Oct 2021	N/A	N/A
2/ 24 Feb 2022	6/ 08 Feb 2022	The updated protocol required modifications to the SAP.	• Updated the time from the last vaccination prior to randomization to the booster vaccination to be at least 5 months for all age groups. • Updated the objectives, estimands, and corresponding analysis methods for the 12- through 17-year age group to have age-matched participants from Study C4591001 as a control group for the primary immunogenicity comparison. • Added an exploratory immunogenicity endpoint (protocol amendment 4).
3/ 29 Sep 2022	11/ 20 Sep 2022	Updated the SAP to reflect changes made in the protocol amendment.	Section 2.1 • Updated the primary immunogenicity objectives, estimands, and endpoint in Table 2. Specifically, updated the comparator group and changed the formal test to descriptive analysis. • Updated the secondary immunogenicity objectives, estimands, and endpoints to present data at 7 days after booster in the first 100 participants. Section 2.2 • Updated the study design and specified that there is no age escalation. Section 3 • Updated the wording in the derivation of maximum severity grade. • Removed the 3-tier approach used to summarize AEs. • Updated the primary immunogenicity endpoints. • Updated the secondary endpoints. • Updated Section 3.4 to describe how the baseline data in C4591001 participants was defined. • Updated Section 3.4.1 by updating how to calculate the age. Section 5 • Removed the immunogenicity hypothesis. All statistical analysis will be descriptive. • Removed the 3-tier method. • Removed the between group comparison.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment/ Date	Rationale	Specific Changes
			• Removed Section 5.2.2.1 (Geometric Mean Ratios). Section 6 • Removed the between group comparison statements and only described GMT, GMFR and seroresponse rate in each group at specified timepoints. • Removed all primary immunogenicity analysis for age groups that are no longer included. • Updated methods to summarize the secondary immunogenicity endpoints. • Updated Section 6.1.1.1.1 by removing the sentence stating that confirmed e-diary errors would be excluded from the analysis. • In Section 6.1.1.1.2, updated Figure section by removing 'level of the booster (third) dose and each age'. • In Section 6.1.1.2.2, the following wording 'In addition, the proportions of participants reporting each prompted systemic event after the booster (third) dose will be summarized by maximum severity level for the primary study.' was removed. • Updated Section 6.1.1.3.1 by removing the 3-tier approach. • Updated Section 6.4, Section 6.5.1.1, Section 6.5.1.2, Section 6.5.2.1 and Section 6.5.4 by removing and/or adding wording. Section 7 • Updated Section 7.2 by adding a paragraph to describe the team's decision to stop this study early. • Updated the analysis timing by removing the 12 months post booster timepoint. Section 8 • Updated the list of references. Throughout • Removed "age group" statements, where applicable, because there is only one age group in the study now.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment/ Date	Rationale	Specific Changes
4/ 25 Sep 2023	12/ 20 Sep 2023	Updated the SAP to reflect changes made in protocol amendment 12.	• In Section 2.1, Section 2.2, Section 3.1.2, Section 6.1.2.1.1, and Section 7.3, the wording related to immunogenicity analysis at the 6 month analysis time point was removed. • In Section 2.1, removed the exploratory immunogenicity objective. • In Section 3.3.1, removed the exploratory endpoint. • In Section 6.3.1, removed the analysis of the exploratory endpoints.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591031 – Substudy C. 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. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary and secondary objective are described in Table 2. The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules (Section 5.3). No other missing information (eg, missing e-diary data) will be imputed in the safety analysis.

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

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To evaluate the safety of a booster dose of BNT162b2 when administered at both 10-µg and 30-µg doses	In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants reporting: • Local reactions for up to 7 days following the booster dose • Systemic events for up to 7 days following the booster dose • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

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

Objectives	Estimands	Endpoints
Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
To describe the immune response to BNT162b2 10 µg and 30 µg given as the third dose in participants 12 through 17 years of age and a third dose of BNT162b2 30 µg in a randomly selected subset of participants 18 through 55 years of age from study C4591001	In participants complying with the key protocol criteria (evaluable participants) from each vaccine group: At baseline (before the third dose) and 1 month after the third dose: • GMTs at each time point • GMFRs from baseline (before the third dose) to each subsequent time point after the third dose • Percentage of participants with seroresponse at each time point after the third dose	• SARS-CoV-2 reference-strain–neutralizing titers
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
To describe the immune response to BNT162b2 10 µg and 30 µg given as the third dose in participants 12 through 17 years of age[a]	At baseline (before the third dose) and 7 days after the third dose: • GMTs at each time point • GMFRs from baseline (before the third dose) to 7 days after the third dose • Percentage of participants with seroresponse at 7 days after the third dose	• SARS-CoV-2 reference-strain–neutralizing titers • SARS-CoV-2 Omicron BA.1-neutralizing titers

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination) for participants in this substudy. If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. For the comparator group of participants from Study C4591001, seroresponse is defined as achieving a ≥4-fold rise from before Dose 3. If the pre-Dose 3 measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

a. This objective is applicable to the immunogenicity analysis of the first approximately 100 participants performed for DMC review.

2.2. Study Design

This is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg or 30 µg. Participants ≥12 years of age who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 5 months (150 days) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive BNT162b2 at either a 10-µg or 30-µg dose level at Visit 301. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results at 7 days after the third dose. A DMC will review safety (e-diary and AE) and immunogenicity data for the first approximately 100 participants with available immunogenicity (~50 participants in each dose level) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of the next age group will occur independently.

As part of Protocol Amendment 11, progression beyond the 12 through 17 years age group will not occur and no further participants will be enrolled.

Serum blood samples will be collected for immunogenicity at baseline, 7 days after the booster (third) dose, 1 month after the booster (third) dose, and 6 months after the booster (third) dose. Up to approximately 150 participants will be randomized in the study.

As part of protocol amendment 12, endpoints and/or analyses that do not pertain to current variant-modified versions of BNT162b2 were removed to expedite remaining testing and to focus on analyses of interest.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Safety Endpoints

- Local reactions (pain at the injection site, redness, and swelling) up to 7 days following the booster (third) dose.
- Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) up to 7 days following the booster (third) dose.
- AEs from the booster (third) dose to 1 month after the booster (third) dose.
- SAEs from the booster (third) dose to 6 months after the booster (third) dose.

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are pain at the injection site, redness, and swelling from Day 1 through Day 7 after the booster (third) dose, where Day 1 is the day of the booster (third) dose. 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 3 defines the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of the booster (third) dose.

Table 3. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

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

Note: Missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary 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 4. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 5.

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

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

Local Reaction	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 should be reported as an AE in the CRF.

For each local reaction after the booster (third) dose, 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 booster [third] dose) as follows:

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

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction (last day of reaction - first day of reaction +1). Resolution of the reaction is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasted 7 days or less, or the day the reaction ended if it continued beyond Day 7 (end date will be collected on the CRF). If there is no known date when the reaction ended, then duration will be considered unknown and set to missing. 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 the reaction with any severity after vaccination.

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.

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of the booster (third) dose. The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.1.1). Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 6 for summary of maximum temperature.

The systemic events will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 5.

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

Table 5. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue/tiredness
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
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
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

Abbreviation: IV = intravenous.

During the 7 days following the booster (third) dose, 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 positive, the symptoms should be recorded as AEs rather than as systemic events in the reactogenicity e-diary.

Potential COVID-19 symptoms that do not overlap with systemic events should be reported as AEs as per Section 8.3 of the protocol.

Oral temperature will be collected in the evening, daily, for 7 days following the booster (third) dose (Days 1 through 7, where Day 1 is the day of the booster [third] dose) and at any time during the 7 days that 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.

Temperatures will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius first for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 6.

If a fever of ≥39.0°C (≥102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor.

Table 6. Scale for Fever

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

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of the booster (third) dose. For the use of antipyretic medication from Day 1 through Day 7 after the booster (third) dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

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

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

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through and including Visit 303 (1 month after the booster [third] dose) for the participants in the study. In addition, any AEs up to 48 hours after any subsequent blood draw will be recorded in the CRF. AEs will be categorized according to MedDRA terms.

The primary endpoints "AEs from booster (third) dose to 1 month after the booster (third) dose" in the study and other supportive AE endpoints will be summarized by system organ class and preferred term at the participant level for each dose level.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after each dose), and AESIs (confirmed diagnosis of myocarditis or pericarditis and confirmed COVID-19 as defined in Section 8.3.8 of the protocol).

AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time of informed consent through and including up to 48 hours after biospecimen collections at Visit 304 (6 months after the booster [third] dose) for the participants in the study. SAEs will be categorized according to MedDRA terms.

The safety endpoints "SAEs from the booster (third) dose to 6 months after the booster (third) dose" in the study will be summarized by system organ class and preferred term at the participant level for each dose level. Additionally, the SAEs will be listed.

3.1.2. Primary Immunogenicity Endpoints

In participants 12 through 17 years of age who received a booster (third) dose of BNT162b2 at 10 or 30 µg and the subset of participants 18 through 55 years of age who received a booster (third) dose of BNT162b2 at 30 µg randomly selected from study C4591001:

- SARS-CoV-2 reference-strain—neutralizing titers at baseline (before the third dose) and 1 month after the third dose.

Titers will be determined using the SARS-CoV-2 neutralizing assay.

Values below the LLOQ will be set to 0.5 × LLOQ for the analysis. The LLOQ value for neutralizing titers will be included in the analysis specification once it is available.

3.2. Secondary Endpoint(s)

In the first approximately 100 randomized participants selected for DMC review of the administrative interim analysis:

- SARS-CoV-2 reference-strain—neutralizing titers at baseline (before the booster [third] dose) and 7 days after the booster (third) dose.

- SARS-CoV-2 Omicron BA.1-neutralizing titers at baseline (before the booster [third] dose) and 7 days after the booster (third) dose.

3.3. Other Endpoint(s)

3.3.1. Exploratory Endpoints

Not applicable

3.4. Baseline Variables

Measurements or samples collected prior to the booster (third) dose in this study and those prior to the third dose in C4591001 (control group) are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at the booster (third) dose (in years), sex (male or female), race (Black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, and not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the booster (third) dose (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 17th birthday, the participant is considered to be 16 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of the booster (third) dose for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant at Visit 1, a physical examination will be performed and any findings recorded in the source documents and, if clinically significant, it will be recorded on the medical history CRF.

3.4.2. 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, then the e-diary will be considered not transmitted.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment to 28 days after study vaccination.

- Prohibited vaccines and medications listed in Section 6.8.1 of the protocol will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

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

3.5. Safety Endpoints

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in Table 7. For the specified criteria in each population definition that are not associated with unblinded information (randomized vaccine or vaccine actually received), data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Table 7. Analysis Sets Description

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Safety	All randomized participants who receive at least 1 dose of the study intervention.
Evaluable immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomized, have a valid and determinate immunogenicity result for the Visit 303 (1 month after the booster [third] dose), have a blood sample collected within an appropriate window (within 28-42 days after the booster [third] dose), and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least a valid and determinate immunogenicity result after vaccination.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of Pfizer'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). Pfizer's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis as described in Section 7.3.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the all-available immunogenicity population if there is over 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.

The safety analyses in the study will be based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received.

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.

The majority of sponsor/Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the testing. Further details can be found in Section 10.9.6.2.2 of the protocol. The timing for statistical analysis is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

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

5.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed for the study as there is no statistical hypothesis.

5.2. General Methods

Unless stated otherwise, "vaccine group" in this document refers to participants receiving either the 10-µg or 30-µg dose. 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, SD, median, minimum, and maximum.

Continuous immunogenicity outcomes of titers will be performed on the natural log scale and the results will be exponentiated and reported in the original scale.

5.2.2.1. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

5.2.2.2. 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 Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. 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

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 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.

The LLOQ for each assay will be provided by Vaccine Research & Development as part of the electronic data transfer or within the Clinical Testing Completion Memo prior to statistical analysis. Assay results above the LLOQ will be reported, and values below the LLOQ, denoted as BLQ, will be imputed as 0.5 × LLOQ for analysis.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting prompted local reactions (pain at the injection site, redness, and swelling) up to 7 days after the booster (third) dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the booster (third) dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; missing values will not be imputed.
- Reporting results: The proportion of participants reporting each local reaction after the booster (third) dose will be summarized by maximum severity level and cumulatively across severity levels. The percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% 2-sided Clopper-Pearson CI will be presented for each vaccine group.

6.1.1.1.2. Supplementary Analyses

As supplementary analyses 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:

- Duration (days) of each local reaction after the booster (third) dose.
- Onset day of each local reaction after the booster (third) dose.

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

Figures:

Bar charts with the proportions of participants for each local reaction throughout the 7 days after the booster (third) dose will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) up to 7 days after the booster (third) dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the booster (third) dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis; missing values will not be imputed.
- Reporting results: The proportion of participants reporting each systemic event after the booster (third) dose will be summarized by maximum severity level and cumulatively across severity levels. The percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% 2-sided Clopper-Pearson CI will be presented for each vaccine group.

6.1.1.2.2. Supplementary Analyses

As supplementary analyses to support the assessment of systemic events, the following endpoints (as defined in Section 3.1.1.2) will be summarized with the same analysis time point and analysis population:

- Duration of each systemic event after the booster (third) dose.
- Onset day of each systemic event after the booster (third) dose.

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

The use of antipyretic medication (Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants for each systemic event throughout the 7 days after the booster (third) dose will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimands: The percentages of participants reporting AEs from the booster (third) dose to 1 month after the booster (third) dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time points: Booster (third) dose to 1 month after the booster (third) dose.
- Analysis methodology: Descriptive statistics.
- Intercurrent events and missing data: No missing values will be imputed except for partial AE start dates (Section 5.3).
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants reporting any AE, by each system organ class and each preferred term within system organ class, will be presented for each vaccine group.

6.1.1.3.2. Supplementary Analyses

As supplementary analyses to support the interpretation of the main analysis results, descriptive summary statistics will also be provided by vaccine group for related AEs, severe AEs, immediate AEs (within the first 30 minutes after the booster [third] dose), and AESIs (defined in Section 8.3.8 of the protocol).

AEs that occurred after informed consent and before the booster (third) dose will not be included in the AE summary tables but will be included in the AE listings.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimands: The percentage of participants reporting SAEs from the booster (third) dose to 6 months after the booster (third) dose (Section 2.1.).
- Analysis set: Safety population (Section 4).
- Analysis time point: Booster (third) dose to 6 months after the booster (third) dose.

- Analysis methodology: Descriptive statistics.

- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants reporting any SAEs, by each system organ class and each preferred term within system organ class, will be presented for each vaccine group.

6.1.2. Primary Immunogenicity Endpoint

6.1.2.1. SARS-CoV-2 Reference-Strain–Neutralizing Titers

In participants 12 through 17 years of age who received a booster (third) dose of BNT162b2 at 10 or 30 µg and the subset of participants 18 through 55 years of age who received a booster (third) dose of BNT162b2 at 30 µg randomly selected from study C4591001.

6.1.2.1.1. Main Analysis

- Estimands:
    - GMT of SARS-CoV-2 reference-strain–neutralizing titers at specific time points for each vaccine group.
    - GMFRs of SARS-CoV-2 reference-strain—neutralizing titers from baseline (before the third dose) to each subsequent time point for each vaccine group.
    - The percentages of participants with seroresponse to reference strain at each time point after the third dose for each vaccine group.
- Analysis set: Evaluable immunogenicity population and all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: baseline (before the third dose) and 1 month after the third dose.
- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at each time point will be provided using the statistical methods described in Section 5.2.2. The GMFRs and the associated 2-sided 95% CIs from baseline to each subsequent time point after the third dose will be provided using the statistical methods described in Section 5.2.2. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. The analyses will be performed in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination) for participants in this substudy. If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. For the comparator group of participants from Study C4591001, seroresponse is defined as achieving a ≥4-fold rise

from before Dose 3. If the pre–Dose 3 measurement is below the LLOQ, the post vaccination measure of ≥4 × LLOQ is considered seroresponse.

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

- Reporting results: GMTs at baseline (before the third dose) and 1 month after vaccination and GMFRs of SARS-CoV-2 reference-strain–neutralizing titers from baseline (before the third dose) to 1 month after the third dose, along with the associated 2-sided 95% CIs, will be provided for each group. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each group.

Figures:

Empirical RCDCs will be presented for the reference-strain–neutralizing titers for each vaccine group. The figure will display curves for each of the dose and time point combinations. Only the evaluable immunogenicity population will be used.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

6.2.1.1. SARS-CoV-2 Reference-Strain– and Omicron BA.1-Neutralizing Titers

In the first approximately 100 randomized participants who received BNT162b2 10 µg and 30 µg as the third dose and included in the administrative interim analysis for DMC review.

6.2.1.1.1. Main Analysis

- Estimands:
    - GMT of SARS-CoV-2 reference-strain– and Omicron BA.1-neutralizing titers at specific time points for each vaccine group.
    - GMFRs of SARS-CoV-2 reference-strain– and Omicron BA.1-neutralizing titers from baseline (before the third dose) to 7 days after the third dose for each vaccine group.
    - The percentages of participants with seroresponse to reference strain and Omicron BA.1 at 7 days after the third dose for each vaccine group.
- Analysis set: all-available immunogenicity population (as applicable) (Table 7).
- Analysis time points: baseline (before the third dose) and 7 days after the third dose.

- Analysis methodology: Descriptive statistics (Section 5.2.2).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: GMTs at each time point and GMFRs from baseline (before the third dose) to 7 days after the third dose, along with the associated 2-sided 95% CIs, will be provided for each group. The percentages of participants with seroresponse at 7 days after the third dose and the associated Clopper-Pearson 95% CIs will be provided for each group.

Figures:

Empirical RCDCs will be presented for the reference-strain–neutralizing titers and Omicron BA.1-neutralizing titers for each vaccine group. The figure will display curves for each of the dose and time point combinations. Only the all-available immunogenicity population will be used.

6.3. Other Endpoint

6.3.1. Exploratory Endpoint

Not applicable.

6.4. Subset Analyses

Subgroup analyses by baseline SARS-CoV-2 will be performed on all primary safety and immunogenicity endpoints (as supplemental analyses).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age, sex, race, and ethnicity, will be summarized using descriptive statistics for each vaccine group and overall. The summary will be provided for the safety population and the evaluable and all-available immunogenicity population.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term 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 system organ class and preferred term level, will be summarized by vaccine group.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received a vaccination, who completed the 1 month after the booster visit, who withdrew before the 1 month after the booster visit, who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment) and overall. The reasons for withdrawal will be those as specified in the database.

Randomized participants excluded from the safety or immunogenicity analysis populations will also be summarized separately, along with the reasons for exclusion, by vaccine group.

6.5.2.2. Blood Samples for Assay

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

6.5.2.3. 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 each dose will be summarized according to the vaccine dose actually received by vaccine group.

The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for all randomized participants. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall.

A listing of participants who received a vaccine other than that to which they were randomized to receive will be produced, if any such incorrect dosing occurs.

A listing of participants showing the randomized vaccine and the vaccine actually received at each dose will be presented.

6.5.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before the booster (third) dose will be listed. The number and percentage of participants receiving each concomitant vaccine after the booster (third) dose of study intervention will be tabulated for each vaccine group for all participants in the safety population. Similar summarization will be done separately for prohibited medications received.

6.6. Safety Summaries and Analyses

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in Section 6.1.1.

7. INTERIM ANALYSES

7.1. Introduction

An administrative interim analysis is planned for each of the younger age groups to inform initiation of enrollment for the next age group. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The interim analysis and timing of the planned analysis and reporting events are described in the sections below.

7.2. Interim Analyses and Summaries

An administrative interim analysis is planned for each of the following age groups:
12 through 17 years, 18 through 30 years, and 31 through 55 years, when 7-day post–booster (third) dose immunogenicity data are available from approximately the first 100 participants (~50 participants in each booster [third] dose–level group).

An unblinded DMC reporting team will review and analyze the safety data (e-diary and AE) and immunogenicity in the first approximately 100 participants with available immunogenicity data in each age group (~50 participants in each dose level of BNT162b2) to guide age escalation 7 days after the booster (third) dose. The first 100 participants will be determined by data management group based on randomization date. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of each age group will occur independently. Only group-level unblinded results will be shared with limited sponsor personnel.

The administrative interim analysis of the first 100 participants in the 12 through 17 years of age group was completed. The DMC did not raise any concerns for age escalation, however as part of Protocol Amendment 11, progression beyond the 12 through 17 years age group will not occur and no further participants will be enrolled. The rationale for this amendment is that a third dose of COVID-19 vaccine has been recommended for all age groups for a considerable period of time (hence the potential substrate for enrollment is essentially

non-existent) and for Fall 2022 the recommended booster vaccine will switch to a bivalent original/Omicron modified vaccine. Both factors contribute to age escalation being operationally unfeasible. Furthermore, since the 30-µg dose level is well tolerated, and in the face of emergence of Omicron and its sublineages for which maximum immune response is desirable, the rationale for a reduced dose level no longer holds.

7.3. Analysis Timing

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

- Safety data through 1 month after the booster (third) dose in each dose-level group.
- Immunogenicity data through 1 month after the third dose for participants enrolled in this study and for the comparator group from the C4591001 study.
- Complete safety analysis approximately 6 months after the booster (third) dose in each dose group.

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. All analyses conducted while the study is ongoing will be performed by an unblinded team.

8. REFERENCES

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

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BLQ	below limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
VOC	variant of concern
WHO	World Health Organization

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