Protocol C4591031 – Substudy F

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

Statistical Analysis Plan (SAP)

Version: 2

Date: 30 Sep 2022

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 03 Mar 2022	7 17 Feb 2022	N/A	N/A
2/ 30 Sep 2022	11 20 Sep 2022	Implemented the changes made in the protocol amendments	1. Added a primary immunogenicity estimand for model-based GMRs in Section 2.2 and provided more details on its analysis in Section 5.2.2.3 and Section 6.1.2.1.1. 2. Updated the seroresponse definition in the footnotes of Table 2. 3. Updated the exploratory endpoints in Section 3.3.1. 4. Removed the analysis for GMRs of SARS-CoV-2 VOC-neutralizing titers to reference-strain–neutralizing titers in Section 5.2.2.3. 5. Added an exploratory immunogenicity estimand for model-based GMRs of neutralizing titers for VOCs not already analyzed as a primary outcome in Section 6.2. 6. Removed "confirmed e-diary errors will be excluded from the analysis" in Section 6.1.1.1.1 and Section 6.1.1.2.1. 7. Removed the analysis timing of 7 days after study vaccination for the safety and immunogenicity data in Section 7.3. 8. Added analysis timing of 3 months after study vaccination for the safety and immunogenicity data in Section 7.3.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591031 – Substudy F. 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, secondary, and exploratory objective in Study C4591031 – Substudy F are described in Table 2 below.

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.

The estimands to evaluate the immunogenicity objective 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.

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

Objectives	Estimands	Endpoints
Primary Safety		
To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a combination of BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose to BNT162b2-experienced participants	In participants receiving at least 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
Primary Immunogenicity		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a combination of BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose in BNT162b2-experienced participants	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponse[a] at each time point • GMRs at each time point after the study vaccination between different vaccine groups	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
Exploratory		
To describe the immune response to any VOCs not already specified		• SARS-CoV-2–neutralizing titers for any VOCs not already specified

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

Objectives	Estimands	Endpoints
To describe the cell-mediated immune response and additional immune response parameters		• T-cell (by ELISPOT) and B-cell characterization • RBD-binding IgG • RBD-binding IgA
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

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.

2.3. Study Design

This is a randomized, observer-blinded substudy to describe the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 OMI (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), given as a single dose. Approximately 180 participants ≥60 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being ≥4 months prior to randomization, will be enrolled in Israel. Participants will be randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2/BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2/BNT162b2 OMI at 60 µg (30 µg each) at Visit 701 as a fourth dose.

Initially, sentinel cohorts (sponsor open-label) of 5 participants per group will be enrolled. An IRC and site representatives will review all reported AEs and reactogenicity e-diary data from the sentinel cohorts collected through Day 7 to allow expanded enrollment of an additional 25 participants per group upon confirmation of an acceptable safety assessment. If the safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2/BNT162b2 OMI (25 µg each).

Table 3 describes the enrollment of the sentinel cohorts and steps to progress to expanded enrollment.

Table 3. Substudy F - Sentinel and Expanded Enrollment

Sentinel Enrollment[a]		
Study Intervention	**Number of Participants**	**Group Number**
BNT162b2 30 µg	5	G1
BNT162b2 60 µg	5	G2
BNT162b2 OMI 30 µg	5	G3
BNT162b2 OMI 60 µg	5	G4
Combination BNT162b2/BNT162b2 OMI 30 µg (15 µg each)	5	G5
Combination BNT162b2/BNT162b2 OMI 60 µg (30 µg each)	5	G6
IRC and site representative reviews all reported adverse event and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.		
Expanded Enrollment[b]		
Study Intervention	**Number of Participants**	**Group Number**
BNT162b2 30 µg	25	G1
BNT162b2 60 µg	25	G2
BNT162b2 OMI 30 µg	25	G3
Study Intervention	**Number of Participants**	**Group Number**
BNT162b2 OMI 60 µg	25	G4
Combination BNT162b2/BNT162b2 OMI 30 µg (15 µg each)	25	G5
Combination BNT162b2/BNT162b2 OMI 60 µg (30 µg each)	25	G6

a. Sentinel cohorts will be sponsor open-label.
b. If the IRC and site representative's safety assessment is considered not to be acceptable, the protocol may be amended to include a further sentinel cohort employing 50-µg dose levels of BNT162b2, BNT162b2 OMI, and a combination of BNT162b2/BNT162b2 OMI (25 µg each).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Safety Endpoints

The primary safety 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/tiredness, 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 vaccination (received in this study) through 1 month after the study vaccination.

- SAEs from vaccination (received in this study) 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, within 7 days after the study 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 4 defines the algorithm to derive the presence of a reaction (yes or no) during the interval within 7 days after the study vaccination.

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

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

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 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 5.

Table 5. Local Reaction Grading Scale

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 reaction should be reported as an AE in the case report form.

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.

For each local reaction after each vaccination, the maximum severity grade will be derived for the e-diary collection period (within 7 days after vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination among the severity grades reported for that local reaction in the e-diary.

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. Resolution is defined as the last day on which the reaction is recorded in the e-diary 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 vaccination (the latter will be collected on the 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 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 within 7 days after vaccination. 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).

The systemic events will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 6.

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 6. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

During the 7 days following the vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or worsened 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 an AE 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 reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period (7 days after each vaccination) 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 7.

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 7. Scale for Fever

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

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will also be recorded in the reactogenicity e-diary daily during the reporting period (7 days after each vaccination). For the use of antipyretic medication within 7 days after vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (7 days after vaccination).
- Presence (yes or no) of use of antipyretic medication on any day (within 7 days after vaccination).

- 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 1 month after the study vaccination. In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded on the CRF. AEs will be categorized according to MedDRA terms. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

The primary safety endpoint "AEs from the study vaccination through 1 month after the study vaccination" and other AE endpoints will be summarized by system organ class and preferred term.

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 vaccination), and AESIs (defined in Section 8.3.8 of the protocol).

3.1.1.5. Serious Adverse Events

SAEs will also be collected from the time of informed consent through 6 months after the study vaccination. SAEs will be categorized according to MedDRA terms.

The safety endpoint "SAEs from the study vaccination through 6 months after the vaccination" will be summarized by system organ class and preferred term. Additionally, SAEs will be listed.

3.1.2. Primary Immunogenicity Endpoints

- SARS-CoV-2 reference-strain–neutralizing titers at each time point.
- SARS-CoV-2 Omicron-neutralizing titers at each time point.

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Endpoint(s)

3.3.1. Exploratory Endpoints

- SARS-CoV-2–neutralizing titers for any VOCs not already specified.
- T-cell (by ELISPOT) and B-cell characterization.
- RBD-binding IgG.
- RBD-binding IgA.
- Confirmed COVID-19 cases.
- Confirmed severe COVID-19 cases.
- Strain sequencing of COVID-19 cases.

3.4. Baseline Variables

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

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables will be collected, including date of birth, sex (male or female), race (Black or African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, and not reported), and racial designation 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 time of the study vaccination (in years) will be derived based on the participant’s birthday. For example, if the vaccination day is 1 day before the participant’s 65th birthday, the participant is considered to be 64 years old.

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 at Visit 701, a physical examination will be performed and any findings will be recorded in the source documents and, if clinically significant, 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 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.

3.4.3. 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 until 28 days following administration of the last study intervention.
- Prohibited medications listed in the protocol, Section 6.8.1, 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 are described in the Primary Safety 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 Table 8. 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 8. Description of the Analysis Sets

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized/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 medical monitor. 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 before any unblinded analysis is carried out.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

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. 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.

The sponsor will be unblinded to the study intervention allocation for the sentinel cohort. For the expanded-enrollment part of the study, 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 10.12.6.2.2. of the protocol. The timing for statistical analysis is specified in Section 7.3.

5.1. Hypotheses and Decision Rules

All objectives in this substudy are descriptive. No hypothesis testing is planned.

5.2. General Methods

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

5.2.1. Analyses for Binary Data

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

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

5.2.2. Analyses for Continuous Data

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

5.2.2.1. Geometric Means

The geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log 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. Geometric Mean Ratios

The relative difference in antibody levels between different vaccine groups, using the BNT162b2 30-µg group as the reference, will be estimated using an ANCOVA model. For each time point after the baseline, log-antibody levels will be modeled using linear regression with the vaccine group as the exposure and the baseline antibody levels as a covariate. The GMR and associated 95% CI will be calculated by exponentiating the difference in least-squares means and the corresponding CIs.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the left side of the step.

5.3. Methods to Manage Missing Data

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 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, 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

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 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: 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: Descriptive statistics for each and any local reaction after the study vaccination in each vaccine group 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 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 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 vaccine group.

Figures:

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

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days 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: 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: Descriptive statistics for each systemic event after the study vaccination in each vaccine group 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 Analyses

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 for the dose by vaccine group.

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

Figures:

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

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from 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 vaccine group.

6.1.1.3.2. Supplemental Analyses

AEs from the study vaccination through 7 days after the study vaccination will be summarized similarly for the IRC and at the corresponding planned analysis timing described in Section 7.3.

Related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.3.8 of the protocol) will also be summarized by vaccine group.

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

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- 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 (received in this study) through 6 months after the study vaccination will be provided for each vaccine group.

6.1.1.4.2. Supplemental Analyses

SAEs from the study vaccination through 7 days after the study vaccination will be summarized similarly for the IRC and at the corresponding planned analysis timing described in Section 7.3.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Primary Immunogenicity Endpoints

6.1.2.1.1. Main Analyses

- Estimands:

    1. GMTs of SARS-CoV-2 Omicron- and reference-strain–neutralizing titers at each time point for each vaccine group.

    2. GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after the study vaccination for each vaccine group.

    3. Percentages of participants with seroresponse to Omicron or the reference strain at each time point for each vaccine group.

    4. GMRs of SARS-CoV-2 Omicron- and reference-strain–neutralizing titers at each time point after the study vaccination between different vaccine groups.

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

- Analysis time points: Before the study vaccination and each subsequent time point after the study vaccination.

- Analysis methodology: GMTs and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.1. The GMFRs and the associated 2-sided 95% CIs from before the study vaccination to each subsequent time point after vaccination will be provided using the statistical methods described in Section 5.2.2.2. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CI for each group will be provided. GMRs and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.3.

- 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 of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group. Model-based GMRs at each time point after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each vaccine group (using the BNT162b2 30-µg group as the reference).

6.2. Exploratory Endpoint(s)

6.2.1. Exploratory Immunogenicity Endpoints

6.2.1.1. SARS-CoV-2–Neutralizing Titers for Any VOCs Not Already Specified

- Estimands:

  1. GMTs and GMFRs of the reference strain or any VOCs not already specified for each vaccine group.

  2. GMRs of the neutralizing titers for VOCs not already analyzed as a primary outcome at specific time point after the study vaccination between different vaccine groups.

- Analyses: GMTs of the reference-strain– or VOC-neutralizing titers and GMFRs from before the study vaccination to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group (Section 5.2.2.1 and Section 5.2.2.2). Model-based GMRs of neutralizing titers for VOCs not already analyzed as a primary outcome at specific time points after the study vaccination, along with the associated 2-sided 95% CIs, may be provided for each vaccine group (using the BNT162b2 30-µg group as the reference) (Section 5.2.2.2 and Section 5.2.2.3).

6.2.1.2. Cell-Mediated Immune Response

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

6.2.1.3. COVID-19 Cases

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

6.3. Subset Analyses

No subset analyses will be conducted.

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, and ethnicity, will be summarized using descriptive statistics for each vaccine group based on the safety population and the evaluable immunogenicity population. Timing of previous doses of BNT162b2 prior to enrollment will also be summarized for each vaccine group.

6.4.1.2. 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 for the safety population.

6.4.2. Study Conduct and Participant Disposition

6.4.2.1. Participant Disposition

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

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

6.4.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for each time point by vaccine 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 each dose 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 and receiving the 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 showing the randomized vaccine and the vaccine actually received at each 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 vaccine 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 Primary Safety 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 in the section below.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analysis Timing

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

- Safety data through 1 month after the study vaccination for each group.
- Immunogenicity data through 1 month after the study vaccination for each group.
- Safety and immunogenicity data through 3 months after study vaccination for each group.
- Complete safety and immunogenicity analysis approximately 6 months after the study vaccination for each 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 for the expanded-enrollment cohort conducted while the study is ongoing will be performed by an unblinded team.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4):404-13.

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

APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomic Therapeutic Chemical
BLQ	below the limit of quantitation
BNT162b2 OMI	BNT162b2 OMICRON (B.1.1.529)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IRC	independent review committee
IWR	interactive Webbased response
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
OMI	Omicron
PBMC	peripheral blood mononuclear cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VOC	variant of concern
WHO	World Health Organization

Document Approval Record

Document Name:	C4591031 Sub Study F Statistical Analysis Plan V2 Clean Copy, 30Sep2022
Document Title:	A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 - SUBSTUDY F

Signed By:	Date(GMT)	Signing Capacity
PPD	30-Sep-2022 20 06 49	Final Approval