Protocol C4591031 – Substudy B

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

Statistical Analysis Plan (SAP)

Version: 2

Date: 08 Dec 2022

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 03 Feb 2022	Protocol amendment 4, 22 Dec 2021	N/A	N/A
2/ 08 Dec 2022	Protocol amendment 11, 20 Sep 2022	The inclusion criteria for Substudy B have been updated to allow inclusion of participants who have received a third dose of BNT162b2 at least 4 months prior to randomization, to support enrollment and to align with current recommendations.	• Section 2.2 (Study Design) has been updated to allow inclusion of participants who have received a booster (third or fourth) dose of BNT162b2 at least 4 months prior to randomization. Timing of prior receipt of BNT162b2 for participants with 2 or 3 prior doses was updated to 4 months prior to randomization. • Section 6.1.1.1.2 has been updated to include supplemental analyses of the number (%) of participants with elevated troponin I results, by sex, age group, and troponin I value range. • Section 6.1.1.2.2 has been updated from "1 month after Vaccination 1 minus 1 month after Vaccination 1 in Sequence 2" to "1 month after Vaccination 1 in Sequence 1 minus 1 month after Vaccination 1 in Sequence 2". • Sections 6.1.1.4.1 and 6.1.1.5.1 have been updated to remove the sentence "Confirmed e-diary errors will be excluded from the analysis" to avoid confusion. • Section 6.4 has been updated from age-to-age group. • Section 6.5.1.1 has been updated to include age group.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591031 – Substudy B. 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 the primary objectives in Substudy B are described in Table 2.

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 Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the frequency of elevated troponin I levels before and after a booster dose of BNT162b2 or placebo	In participants receiving 1 dose of study intervention, the percentage of participants with elevated troponin I levels before and at subsequent time points after a booster dose of BNT162b2 or placebo	• Troponin I level
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each vaccination • Systemic events for up to 7 days following each vaccination • AEs within 1 month after each vaccination • SAEs within 1 month after each vaccination	• 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

2.2. Study Design

This is a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥12 years of age to ≤30 years of age who have received 2 or 3 prior doses of BNT162b2 (30-µg doses), with their last dose at least 4 months (120 days) prior to randomization, will be enrolled. Participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at Visit 201 (Vaccination 1) and the alternative at Visit 203 (Vaccination 2), 4 weeks later. Randomization will be stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Approximately 1500 participants will be randomized in the study.

Serum blood samples will be collected for troponin I testing before each vaccination, 2 to 5 days after each vaccination, and 1 month after the second vaccination. Participants will be observed for 30 minutes after each vaccination and any reactions occurring during that time will be recorded as AEs. Local reactions, systemic events (including fever), and use of antipyretic medication occurring within 7 days after each vaccination will be collected via a provided e-diary (or e-diary application). AEs and SAEs will be collected from the signing of informed consent through and including Visit 205 (1 month after Vaccination 2). In addition, any AEs occurring up to 48 hours after any subsequent blood draw must be recorded in the CRF.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Safety Endpoints

- Troponin I levels before and at subsequent time points after a vaccination.
- Local reactions (pain at the injection site, redness, and swelling) for up to 7 days following each 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 following each vaccination.
- AEs within 1 month after each vaccination.
- SAEs within 1 month after each vaccination.

3.1.1.1. Troponin I Level

A blood sample will be collected to obtain a serum sample for troponin testing before each vaccination, 2 to 5 days after each vaccination, and 1 month after the second vaccination. Elevated troponin I levels are defined as >35 ng/L in male participants or >17 ng/L in female participants. Other cutoff values for abnormality may also be applied.

3.1.1.2. 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 each vaccination, where Day 1 is the day of each 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 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 each vaccination.

Table 3. 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 (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 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 4.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify Pfizer and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[a]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

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

For each local reaction after each 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 each dose) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) 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 lasted 7 days or less, or the day the reaction ended if it continued beyond Day 7 (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). However, if a reaction is ongoing at the time of a subsequent dose, the end date/day for the ongoing event would be the date/day that the next dose is administered, which will be used for the duration computation. 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.

3.1.1.3. 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 each 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 3.1.1.2). Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 6.

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 Pfizer and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

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

Table 5. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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 vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should be assessed by the investigator.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if 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 evening, daily, for 7 days following each vaccination (Days 1 through 7, where Day 1 is the day of 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 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 Pfizer and, if it is determined to be related to the vaccination, further vaccinations will be discontinued in that participant.

Table 6. Ranges for Fever

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

3.1.1.4. 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 each vaccination. For the use of antipyretic medication from Day 1 through Day 7 after each vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.2), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7) for each vaccination
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7) for each 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.

3.1.1.5. Adverse Events

AEs will be collected from the time of informed consent through and including Visit 205 (1 month after Vaccination 2). 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 endpoint "AEs within 1 month after each vaccination" and other supportive AE endpoints will be summarized by system organ class and preferred term at the participant 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 vaccination), and AESIs (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.

3.1.1.6. Serious Adverse Events

SAEs will also be collected from the time of informed consent through and including Visit 205 (1 month after Vaccination 2). SAEs will be categorized according to MedDRA terms.

The primary safety endpoint "SAEs within 1 month after each vaccination" will be summarized by system organ class and preferred term at the participant level. Additionally, the SAEs will be listed.

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Endpoint(s)

Not applicable.

3.4. Baseline Variables

Measurements or samples collected prior to Vaccination 1 at Visit 201 are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at Vaccination 1 (in years), sex (male or female), BMI, race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, 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 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 19th birthday, the participant is considered to be 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at booster vaccination 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, a physical examination will be performed and any findings will be recorded in the source documents and clinically significant findings, if any, 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 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 on the CRF:

- Any vaccinations received from 28 days prior to study enrollment until 28 days following administration of the last study intervention.
- Prohibited 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 WHO DDE.

3.5. Safety Endpoints

Troponin I level, local reactions, systemic events, AEs, and SAEs have been described in the Primary Safety Endpoints section (Section 3.1.1).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Safety	All participants who receive at least 1 dose of the study intervention.

The important protocol deviations will be determined by the medical monitor. The safety analyses in the study will be based on the safety population. Participants will be summarized by vaccine sequence as well as the vaccine group according to the study interventions they 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 Pfizer staff will be blinded to study intervention allocation. The blinded study team will become unblinded to the study randomization information at the time of the database release of the study.

5.1. Hypotheses and Decision Rules

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

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

5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise. Unless stated otherwise, "vaccine sequence" in this document refers to the participants receiving BNT162b2 followed by placebo or vice versa, and "vaccine group" refers to participants receiving BNT162b2 or placebo combining Sequence 1 and Sequence 2.

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]

For the between-group comparison of binary endpoints, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method.[2]

For the within-group comparison of binary endpoints, the 2-sided 95% CI for the difference in percentages will be calculated using the adjusted Wald interval as described by Agresti and Min[3] (2005) for comparing matched proportions.

This is done by adding 0.5 to each cell according to Agresti and Min's method, and thus 2 is added to the total n (see Table 7). Table 7 gives a representation of the cells in a 2 × 2 table for comparing percentages of elevated troponin I levels at different time points (ie, after receiving BNT162b2 and after receiving placebo, or before and after receiving vaccination).

Table 7. Illustration of Cells in a 2 × 2 Table for Matched Proportions

Time Point 1	Time Point 2		
	Participants with elevated troponin	Participants without elevated troponin	Total
Participants with elevated troponin	a	b	a+b (p1)
Participants without elevated troponin	c	d	c+d
Total	a+c (p2)	b+d	n

The comparison of interest, p2-p1, can be written as (a+c)/n – (a+b)/n = (c-b)/n. The 2-sided 95% CI for the difference in matched proportions using the adjusted Wald method is:

$$\frac{C^* - b^*}{n^*} \pm \left(^{a/2}\frac{\sqrt{(b^* + C^*) - \frac{(C^* - b^*)^2}{n^*}}}{n^*}\right)$$

with $b^* = b + 0.5;\ C^* = C + 0.5;\ n^* = n + 2;\ a = 0.05$

5.2.2. Analyses for Continuous Endpoints

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

5.3. 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.

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. Percentage of Participants With Elevated Troponin I Levels

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants with elevated troponin I levels before and at subsequent time points after a vaccination.

- Analysis set: Safety population (Section 4). The analysis will be limited to participants with valid and determinate troponin I results from the blood sample collected within the protocol-defined window at each visit after vaccination (Visit 202: 2-5 days after Vaccination 1; Visit 203: 28-35 days after Vaccination 1; Visit 204: 2-5 days after Vaccination 2; Visit 205: 28-35 days after Vaccination 2).

- Analysis time points: Before, 4 days after, and 1 month after the administration of BNT162b2 or placebo.

- Analysis methodology: The percentages of participants with elevated troponin I levels and the associated 2-sided 95% CIs will be calculated using the Clopper-Pearson method (Section 5.2.1).

- Intercurrent events and missing data: Missing values will not be imputed.

- Reporting results: Counts, percentages, and associated 95% CIs for participants with elevated troponin I levels at before, 4 days after, and 1 month after administration of BNT162b2 or placebo will be provided for Sequence 1 and Sequence 2 separately and combined, by vaccine group.

6.1.1.1.2. Supplementary Analyses

The same analysis described in Section 6.1.1.1.1 will also be performed using all available troponin I results at each visit regardless of the protocol-defined window.

In addition, as supplementary analyses to support the interpretation of the main analysis results, the number (%) of participants with elevated troponin I results, by sex, age group, and troponin I value range, will also be provided.

6.1.1.2. Difference in Troponin I Level Between Vaccine Groups

6.1.1.2.1. Main Analysis

- Estimand: The difference in percentages of participants with elevated troponin I levels between vaccine groups after a vaccination.

- Analysis set: Safety population (Section 4). The analysis will be limited to participants with valid and determinate troponin I results from the blood sample collected within the protocol-defined window at each visit after vaccination (Visit 202: 2-5 days after Vaccination 1; Visit 203: 28-35 days after Vaccination 1; Visit 204: 2-5 days after Vaccination 2; Visit 205: 28-35 days after Vaccination 2).

- Analysis time points: 4 Days and 1 month after the administration of BNT162b2 or placebo. This analysis will be limited to participants with troponin I level measurements after both vaccinations.

- Analysis methodology: The difference in percentages of participants with elevated troponin I levels between vaccine groups and the associated 2-sided 95% CIs will be calculated using the adjusted Wald interval by Agresti and Min[3] (Section 5.2.1).

- Intercurrent events and missing data: Missing values will not be imputed.

- Reporting results: The difference in percentages of participants with elevated troponin I levels between BNT162b2, and placebo and the associated 95% CIs will be provided at 2 time points after vaccination (4 days after BNT162b2 minus 4 days after placebo, or 1 month after BNT162b2 minus 1 month after placebo) combining Sequence 1 and Sequence 2.

6.1.1.2.2. Supplementary Analyses

The same analysis described in Section 6.1.1.2.1 will also be performed using all available troponin I results at each visit regardless of the protocol-defined window.

In order to detect a significant carryover effect after BNT162b2, Fisher's exact test[4] will be performed to compare the percentages of Sequence 2 participants with elevated troponin I levels at 4 days and 1 month after placebo versus the percentages of Sequence 1 participants with elevated troponin I levels at 4 days and 1 month after placebo.

In addition, the difference in percentages of participants with elevated troponin I levels after the first vaccination between Sequence 1 and Sequence 2 (ie, 4 days after Vaccination 1 in Sequence 1 minus 4 days after Vaccination 1 in Sequence 2, 1 month after Vaccination 1 in Sequence 1 minus 1 month after Vaccination 1 in Sequence 2) and associated 95% CIs will be calculated based on the Miettinen and Nurminen method.[2]

6.1.1.3. Change in Troponin I Level From Before Vaccination to Subsequent Time Points After Vaccination

6.1.1.3.1. Main Analysis

- Estimand: The difference in percentages of participants with elevated troponin I levels measured before and after each vaccination (BNT162b2 or placebo).

- Analysis set: Safety population (Section 4). The analysis will be limited to participants with valid and determinate troponin I results from the blood sample collected within the protocol-defined window at each visit after vaccination (Visit 202: 2-5 days after Vaccination 1; Visit 203: 28-35 days after Vaccination 1; Visit 204: 2-5 days after Vaccination 2; Visit 205: 28-35 days after Vaccination 2).

- Analysis time points: 4 Days and 1 month after the administration of BNT162b2 or placebo. This analysis will be limited to participants with troponin I level measurements at both time points (before vaccination and 4 days or 1 month after vaccination).

- Analysis methodology: The 2-sided 95% CI for the difference in percentages will be calculated using the adjusted Wald interval as described by Agresti and Min (2005)[3] for comparing matched proportions (Section 5.2.1).

- Intercurrent events and missing data: Missing values will not be imputed.

- Reporting results: The difference in percentages of participants with elevated troponin I levels from before and after each vaccination (4 days and 1 month after BNT162b2 minus before BNT162b2, 4 days and 1 month after placebo minus before placebo) and associated 95% CI will be presented by vaccine group, combining Sequence 1 and Sequence 2.

6.1.1.3.2. Supplementary Analyses

The same analysis described in Section 6.1.1.3.1 will also be performed using all available troponin I results at each visit regardless of the protocol-defined window.

6.1.1.4. Local Reactions

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting prompted local reactions (pain at the injection site, redness, and swelling) within 7 days after each vaccination (Section 2.1).

- Analysis set: Safety population (Section 4).

- Analysis time point: Within 7 days after each 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 each vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.

- Reporting results: The proportion of participants reporting each and any local reaction after BNT162b2 or placebo administration 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 reported for Sequence 1 and Sequence 2 separately and combined, by vaccine group.

6.1.1.4.2. Supplementary Analyses

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

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

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine sequence and for each vaccine group combining Sequence 1 and Sequence 2.

Figures:

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

6.1.1.5. Systemic Events

6.1.1.5.1. 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) within 7 days after each vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each 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 each vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: The proportion of participants reporting each and any systemic event after BNT162b2 or placebo 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 reported for Sequence 1 and Sequence 2 separately and combined, by vaccine group.

6.1.1.5.2. Supplementary Analyses

As supplementary analyses to support the assessment of systemic events, the following endpoints (as defined in Section 3.1.1.3) will be summarized with the same analysis time point and analysis population:

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

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each sequence and for Sequence 1 and Sequence 2 combined, by vaccine group.

The use of antipyretic medication (see Section 3.1.1.4) 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 7 days after each vaccination will be plotted for Sequence 1 and Sequence 2 separately and combined, by vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.6. Adverse Events

6.1.1.6.1. Main Analysis

- Estimand: The percentages of participants reporting AEs within 1 month after each vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 1 month after each vaccination.
- Analysis methodology: Descriptive statistics described in Section 5.2.1.
- Intercurrent events and missing data: No missing values will be imputed except for partial AE start dates (Section 5.3).

- Reporting results: AEs will be categorized according to MedDRA terms. 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 system organ class and preferred term within system organ class, will be presented for Sequence 1 and Sequence 2 separately and combined, by vaccine group.

6.1.1.6.2. Supplementary Analyses

As supplementary analyses to support the interpretation of the main analysis results, descriptive summary statistics will also be provided after each vaccination for Sequence 1 and Sequence 2 separately and combined, by vaccine group, for related AEs, severe AEs, and AESIs (defined in Section 8.3.8 of the protocol) collected during 1 month after each vaccination. Immediate AEs (within the first 30 minutes after each vaccination) will also be summarized for each vaccination for Sequence 1 and Sequence 2 separately and combined, by vaccine group, if the number of immediate AEs is sufficiently large; otherwise, they will be listed only.

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

6.1.1.7. Serious Adverse Events

6.1.1.7.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs within 1 month after each vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 1 month after each vaccination.
- Analysis methodology: Descriptive statistics described in Section 5.2.1.
- Reporting results: SAEs will be categorized according to MedDRA terms. 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 system organ class and preferred term within system organ class, will be presented for Sequence 1 and Sequence 2 separately and combined, by vaccine group.

6.2. Secondary Endpoint(s)

Not applicable.

6.3. Other Endpoint(s)

Not applicable.

6.4. Subset Analyses

Subgroup analyses by age group, sex, race, and ethnicity may be performed on primary safety endpoints (as supplementary analyses).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age, age group, sex, race, ethnicity, and classification of BMI, will be summarized for the safety population for each sequence and overall.

In addition, the time between the last dose of BNT162b2 prior to randomization and the first booster vaccination will be summarized for the safety population for each sequence and overall.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by sequence and overall, for the safety population.

6.5.2. Study Conduct and Participant Disposition

A listing of participants with protocol deviations will be presented.

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 Vaccinations 1 and 2, who completed the follow-up visits, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by sequence (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

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

6.5.2.2. Blood Samples for Assay

The number and percentage of participants assigned to study intervention and providing blood samples within and outside of protocol-specified time frames will be tabulated separately for each time point by vaccine sequence.

6.5.2.3. Transmission of E-Diaries

The numbers and percentages 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 will be summarized according to the vaccine sequence actually received. The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

The numbers and percentages of participants randomized and receiving each study vaccination, receiving Vaccination 2 within the protocol-specified time frame, and receiving Vaccination 2 before and after the specified time frame will be tabulated for each sequence and overall, for all randomized participants. The denominator for the percentages is the total number of randomized participants in the given sequence or overall.

In addition, the relation of randomized vaccine sequence to vaccine sequence actually received will be presented as a cross tabulation of the vaccine sequence actually received versus the randomized vaccine sequence.

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

6.5.4. Prior/Concomitant Medications and Vaccinations

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days prior to study enrollment until 28 days following administration of the last study intervention will be listed. The number and percentage of participants receiving each concomitant vaccine after Vaccination 1 will be tabulated by vaccine sequence. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analysis

Troponin I level, local reaction, systemic reaction, AE, and SAE summaries and analyses are described under Primary Endpoint(s) in Section 6.1.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. Only 1 analysis will be performed at the completion of the study.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analysis Timing

Final statistical analyses are planned to be carried out after the complete study data are available and the database is locked.

7.4. Data Monitoring Committee

This substudy will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail. The DMC will be responsible for ongoing monitoring of the safety data throughout the study according to the charter.

The recommendations made by the DMC will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators as appropriate.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
ICD	informed consent document
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO DDE	World Health Organization Drug Dictionary Enhanced

Document Approval Record

Document Name:	C4591031 Sub Study B Statistical Analysis Plan Clean Copy V2, 08Dec2022
Document Title:	A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 - SUBSTUDY B

Signed By:	Date(GMT)	Signing Capacity
PPD	08-Dec-2022 14 22 54	Final Approval