**Protocol C4591031 – Substudy E**

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

## Statistical Analysis Plan (SAP)

**Version:** 3

**Date:** 01 Sep 2022

[redacted]

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**APPENDICES**

# 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version/Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1/ 07 Mar 2022 | PA7-17 Feb 2022 | N/A | N/A |
| 2/ 20 May 2022 | PA9-03 May 2022 | Added 18- to 55-year age cohort and modified objectives | 1. Added 18- to 55-year age cohort with 3 treatment arms (bivalent BNT162b2 and BNT162b2 OMI at 60 µg [30 µg each], bivalent BNT162b2 and BNT162b2 OMI at 30 µg [15 µg each], and BNT162b2 OMI at 60 µg at 3:1:2 ratio) in Section 2.3.<br>2. Modified primary, secondary, and exploratory objectives, estimands, and endpoints in Section 2.2 and Section 3 Modified seroresponse definition in Section 2.2<br>3. Modified hypotheses, decision rules, and multiplicity analysis in Section 5.1<br>4. Modified analyses in Section 6 accordingly based on PA9<br>5. Removed analysis timing at 7 days for safety and immunogenicity in Section 7.3 |
| 3/ 01 Sep 2022 | PA10-22 Jul 2022 | Clarified the subset of participants to be selected for the exploratory objective | 1. Modified the comparison group for the immune response of the 18- to 55-year group in Section 2.2 in footnote “b” for Table 2<br>2. Clarified days of 5 to 12 months in Section 2.3<br>3. Defined the elevated troponin I levels in Section 3.1.1.6 |

**Table 1. Summary of Changes**

| Version/Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| | | | 4. Clarified that the primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated by the statistical hypotheses, and clarified the immunogenicity objectives for participants 18 to 55 years of age are descriptive only, in Sections 5.1 and 5.1.2<br>5. Clarified that no multiplicity adjustment is applied to 18-55 years in Section 5.1.2<br>6. Clarified the sensitivity analysis in Section 5.2.1<br>7. Deleted "Confirmed e-diary errors will be excluded from the analysis" in Section 6.1.1.1.1 |

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591031 – Substudy E. 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 objectives in Substudy E 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 will be imputed in the safety analysis.

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.

**Table 2. List of Primary, Secondary, 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 bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose to BNT162b2-experienced participants >55 years of age | In participants receiving at least 1 dose of study intervention, the percentage of participants reporting:<br>• Local reactions for up to 7 days following the study vaccination<br>• Systemic events for up to 7 days following the study vaccination<br>• AEs from the study vaccination through 1 month after the study vaccination<br>• SAEs from the study vaccination through 6 months after the study vaccination | • Local reactions (pain at the injection site, redness, and swelling)<br>• Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)<br>• AEs<br>• SAEs |
| To describe the safety and tolerability profile of BNT162b2 OMI 60 µg and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants 18 to 55 years of age | In participants receiving at least 1 dose of study intervention, the percentage of participants reporting:<br>• Local reactions for up to 7 days following the study vaccination<br>• Systemic events for up to 7 days following the study vaccination<br>• AEs from the study vaccination through 1 month after the study vaccination<br>• SAEs from the study vaccination through 6 months after the study vaccination<br>• Percentage of participants with elevated troponin I levels before and 3 days after study vaccination (sentinel cohort only) | • Local reactions (pain at the injection site, redness, and swelling)<br>• Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)<br>• AEs<br>• SAEs<br>• Troponin I level (sentinel cohort only) |

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

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary Immunogenicity** | | |
| G3vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:<br>• GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants<br>• The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants | • SARS-CoV-2 Omicron-neutralizing titers |
| G4vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:<br>• GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants<br>• The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants | • SARS-CoV-2 Omicron-neutralizing titers |
| G5vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:<br>• GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants<br>• The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants | • SARS-CoV-2 Omicron-neutralizing titers |

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

| Objectives | Estimands | Endpoints |
|---|---|---|
| G6vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:<br>• GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants<br>• The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants | • SARS-CoV-2 Omicron-neutralizing titers |
| **Secondary Immunogenicity** | | |
| G5vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:<br>• GMR of the reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants | • SARS-CoV-2 reference-strain–neutralizing titers |
| G6vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection:<br>• GMR of the reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants | • SARS-CoV-2 reference-strain–neutralizing titers |
| To demonstrate the 'super' superiority of anti-Omicron immune responses after 1 dose of BNT162b2 OMI at 30 µg (G3vG1B), BNT162b2 OMI at 60 µg (G4vG1B), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (G5vG1C), or bivalent BNT162b2 and BNT162b2 OMI at 60 µg (G6vG1C) compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age | Same as GMR estimand of G3vG1A, G4vG1A, G5vG1A, and G6vG1A | • SARS-CoV-2 Omicron-neutralizing titers |

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

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Exploratory** | | |
| To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and a bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose in BNT162b2-experienced participants >55 years of age | • GMT at each time point<br>• GMFRs from before the study vaccination to subsequent time points<br>• Percentages of participants with seroresponsea at each time point | • SARS-CoV-2 Omicron-neutralizing titers<br>• SARS-CoV-2 reference-strain–neutralizing titers |
| To describe immune response to bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg), BNT162b2 OMI 60 µg, and BNT162b2 30 µg[b] given as a fourth dose in BNT162b2-experienced participants 18 to 55 years of age | • GMT at each time point<br>• GMFRs from before the study vaccination to subsequent time points<br>• Percentages of participants with seroresponse[a] at each time point | • SARS-CoV-2 Omicron-neutralizing titers<br>• SARS-CoV-2 reference-strain–neutralizing titers |
| To describe the immune response to the reference strain and VOCs for participants[c] in sentinel cohorts of each age group | | SARS-CoV-2–neutralizing titers for the reference strain and VOCs |
| To describe the immune response to any VOCs not already specified in each age group | | SARS-CoV-2–neutralizing titers for any VOCs not already specified |
| To describe confirmed COVID-19 and severe COVID-19 cases in each age group | | • Confirmed COVID-19 cases<br>• Confirmed severe COVID-19 cases<br>• Strain sequencing of COVID-19 cases |
| To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group for each age group | | |

a. Seroresponse is defined as achieving ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of >4 × LLOQ is considered seroresponse.
b. A subset of the youngest 150 participants from the >55-year-old group in Substudy E who have received bivalent BNT162b2 30 µg as fourth dose will be selected for this objective.
c. This subset of participants will not contribute to the assessment of primary immunogenicity objectives.

## 2.3. Study Design

This is a randomized, observer-blinded substudy to evaluate 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 (60 µg [30 µg each], given as a single dose). Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization, will be enrolled at investigator sites in the US only. Participants >55 years of age 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, combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 601 as a fourth dose. Participants 18 to 55 years of age will be randomized to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or BNT162b2 OMI at 60 µg at Visit 601 as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open label) of 20 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 90 sentinel cohort participants. An IRC 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 300 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 combination of BNT162b2 and BNT162b2 OMI (25 µg each).

For participants 18 to 55 years of age, sentinel cohorts (sponsor open-label) of 30 participants per group will be enrolled. E-diary data from Day 1 and Day 2 for the first 15 participants enrolled in the sentinel cohort (5 per group) will be evaluated prior to enrollment of the remaining 75 sentinel-cohort participants. An IRC will review all reported AEs, reactogenicity e-diary data, and troponin levels from the sentinel cohorts collected through Day 7 to allow expanded enrollment upon confirmation of an acceptable safety assessment. An additional 900 participants will be enrolled and randomized in 3:1:2 ratio to receive bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg.

Table 3 and Table 4 describe the enrollment of the sentinel cohorts and steps to progress to expanded enrollment for the >55-year age groups and 18- to 55-year age groups, respectively.

## Table 3. Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment

| Initial-Sentinel Enrollment[a] | | |
|---|---|---|
| **Study Intervention** | **Number of Participants** | **Group Number** |
| BNT162b2 30 µg (participants >55 years of age) | 5 | G1 |
| BNT162b2 60 µg (participants >55 years of age) | 5 | G2 |
| BNT162b2 OMI 30 µg (participants >55 years of age) | 5 | G3 |
| BNT162b2 OMI 60 µg (participants >55 years of age) | 5 | G4 |
| Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[b] (participants >55 years of age) | 5 | G5 |
| Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[b] (participants >55 years of age) | 5 | G6 |
| | | |
| ***Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants*** | | |
| | | |
| **Expanded-Sentinel Enrollment[a]** | | |
| **Study Intervention** | **Number of Participants** | **Group Number** |
| BNT162b2 30 µg (participants >55 years of age) | 15 | G1 |
| BNT162b2 60 µg (participants >55 years of age) | 15 | G2 |
| BNT162b2 OMI 30 µg (participants >55 years of age) | 15 | G3 |
| BNT162b2 OMI 60 µg (participants >55 years of age) | 15 | G4 |
| Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[b] (participants >55 years of age) | 15 | G5 |
| Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[b] (participants >55 years of age) | 15 | G6 |
| | | |
| ***IRC review of 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[c]** | | |
| **Study Intervention** | **Number of Participants** | **Group Number** |
| BNT162b2 30 µg (participants >55 years of age) | 300 | G1 |
| BNT162b2 60 µg (participants >55 years of age) | 300 | G2 |
| BNT162b2 OMI 30 µg (participants >55 years of age) | 300 | G3 |
| BNT162b2 OMI 60 µg (participants >55 years of age) | 300 | G4 |

## Table 3. Substudy E – Participants >55 Years of Age – Sentinel and Expanded Enrollment

| Study Intervention | Number of Participants | Group Number |
|---|---|---|
| Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each)[d] (participants >55 years of age) | 300 | G5 |
| Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each)[d] (participants >55 years of age) | 300 | G6 |

Abbreviation: IRC = independent review committee.

a. Sentinel cohorts will be sponsor open label.
b. Initial- and expanded-sentinel enrollment participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive doses that are prepared at the investigator site from 1 vial each of diluted BNT162b2 vaccine and BNT162b2 OMI vaccine.
c. If the IRC'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 and BNT162b2 OMI (25 µg each).
d. Expanded-enrollment participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required.

## Table 4. Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment

| **Initial-Sentinel Enrollment**[a,b] | | | |
|---|---|---|---|
| **Group** | **Study Intervention** | **Number of Participants** | **Group Number** |
| 7 | Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age) | 5 | G7 |
| 8 | Bivalent BNT162b2 and BNT162b2 30 µg (15 µg each) (participants 18 to 55 years of age) | 5 | G8 |
| 9 | BNT162b2 OMI 60 µg (participants 18 to 55 years of age) | 5 | G9 |
| | | | |
| ***Study team review of Day 1 and Day 2 e-diary reactogenicity data from sentinel-cohort participants*** | | | |
| | | | |
| **Expanded-Sentinel Enrollment** | | | |
| **Group** | **Study Intervention** | **Number of Participants** | **Group Number** |
| 7 | Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age) | 25 | G7 |
| 8 | Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age) | 25 | G8 |
| 9 | BNT162b2 OMI 60 µg (participants 18 to 55 years of age) | 25 | G9 |
| | | | |
| ***IRC review of all reported AE and reactogenicity e-diary data from the sentinel cohorts collected through Day 7. Expanded enrollment to commence upon confirmation of an acceptable safety assessment.*** | | | |
| | | | |

**Table 4. Substudy E – Participants 18 to 55 Years of Age – Sentinel and Expanded Enrollment**

| Expanded Enrollment[c] | | | |
|---|---|---|---|
| **Group** | **Study Intervention** | **Number of Participants** | **Group Number** |
| 7 | Bivalent BNT162b2 and BNT162b2 OMI 60 µg (30 µg each) (participants 18 to 55 years of age) | 450 | G7 |
| 8 | Bivalent BNT162b2 and BNT162b2 OMI 30 µg (15 µg each) (participants 18 to 55 years of age) | 150 | G8 |
| 9 | BNT162b2 OMI 60 µg (participants 18 to 55 years of age) | 300 | G9 |

Abbreviation: IRC = internal review committee.

a. Sentinel cohorts will be sponsor open-label.

b. Participants randomized to bivalent BNT162b2 and BNT162b2 OMI 30 µg and 60 µg will receive the doses from a single 100-µg/mL vial of BNT162b2 bivalent [Wild Type and Omicron (B.1.1.529)] preformulated vaccine suspension for injection. No dilution is required.

c. If the IRC'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 and 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 the study vaccination through 1 month after the study vaccination
- SAEs from the study vaccination through 6 months after the study vaccination
- Troponin I level at before and 3 days after study vaccination (sentinel cohort 18-55 years of age only)

#### 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 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 5 defines the algorithm to derive the presence of a reaction (yes or no) during the interval within 7 days after the study vaccination.

**Table 5. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for the Study Vaccination**

| Variable | Yes (1) | No (0) |
|---|---|---|
| Presence of each local reaction on any day | Participant reports the reaction as "yes" on any day (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 6. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 6.

**Table 6. 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 |

**Table 6. Local Reaction Grading Scale**

| Local Reaction | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life-Threatening (Grade 4)[a] |
|---|---|---|---|---|
| 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 qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale.

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 the study vaccination, the maximum severity grade will be derived for the e-diary collection period (within 7 days after the study 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, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after the study vaccination. The derivations for systemic events will be handled 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 7.

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

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if 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 protocol Section 8.3.

Oral temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period (7 days after the study 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 (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 8.

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 8. Scale 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) |

### 3.1.1.3. 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 the study vaccination). For the use of antipyretic medication within 7 days after the study vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1 where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (7 days after the study vaccination)
- Presence (yes or no) of use of antipyretic medication on any day (within 7 days after the study 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 the study 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 approximately 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 study vaccination" will be summarized by system organ class and preferred term. Additionally, SAEs will be listed.

#### 3.1.1.6. Troponin I Level

Troponin I level will be collected at screening before study vaccination and 3 days after study vaccination for sentinel cohort participants 18 to 55 years of age. Elevated troponin I level is defined as >35 ng/L in males or >17 ng/L in females.

Percentage of participants with elevated troponin I levels will be summarized.

### 3.1.2. Primary Immunogenicity Endpoints

- G3vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg (Group 3) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G4vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg (Group 4) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G5vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg (Group 5) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G6vG1A: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg (Group 6) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

### 3.2. Secondary Endpoint(s)

- G5vG1B: SARS-CoV-2 reference-strain–neutralizing titers after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg (Group 5) compared to after 1 dose of BNT162b2 at 30 µg (Group 1) given as a fourth dose in BNT162b2-experienced participants >55 years of age.

- G6vG1B: SARS-CoV-2 reference-strain–neutralizing titers after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg (Group 6) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G3vG1B: SARS-CoV-2 Omicron-neutralizing titers after 1 dose of BNT162b2 OMI at 30 µg (Group 3) compared to after 1 dose of BNT162b2 at 30 µg (Group 1) given as a fourth dose in BNT162b2-experienced participants >55 years of age.

- G4vG1B: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg (Group 4) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

- G5vG1C: SARS-CoV-2 Omicron-neutralizing titers after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg (Group 5) compared to after 1 dose of BNT162b2 at 30 µg (Group 1) given as a fourth dose in BNT162b2-experienced participants >55 years of age.

- G6vG1C: SARS-CoV-2 Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg (Group 6) and those at 1 month after 1 dose of BNT162b2 at 30 µg (Group 1) given as the fourth dose in BNT162b2-experienced participants >55 years of age.

## 3.3. Other Endpoint(s)

### 3.3.1. Exploratory Endpoints

- SARS-CoV-2 Omicron-neutralizing titers at each time point

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

- SARS-CoV-2–neutralizing titers for the reference strain and VOCs in sentinel cohorts

- SARS-CoV-2–neutralizing titers for any VOCs not already specified

- Confirmed COVID-19 cases

- Confirmed severe COVID-19 cases

- Strain sequencing of COVID-19 cases

- Cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and Omicron in a subset of participants with PBMC samples collected in each group

## 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/African American, American Indian, or Alaskan native, Asian, Native Hawaiian, or other Pacific Islander, White, multiracial, and not reported), ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported), and BMI. In cases where more than 1 category is selected for race, the participant would be counted under the category “multiracial” for analysis.

Age at the time of the study vaccination (in years) will be derived based on the participant's birthday. For example, if the study vaccination day is 1 day before the participant's 60th birthday, the participant is considered to be 59 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 601, 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.

#### 3.4.1.1. 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.

#### 3.4.1.2. 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 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, SAEs and Troponin I level have been described above 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 the table below. Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

**Table 9. Analysis Sets Description**

| 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 cohorts. 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 the study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 10.11.6.2.2. The timing for statistical analysis is specified in Section 7.3.

## 5.1. Hypotheses and Decision Rules

The primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated by the following statistical hypotheses. The immunogenicity objectives for participants 18 to 55 years are descriptive only.

### 5.1.1. Immunogenicity Hypotheses

**Superiority and Noninferiority of Omicron Immune Responses**

The primary immunogenicity objective is to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti–Omicron immune response induced by a dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti–Omicron immune response elicited by a dose of BNT162b2 at 30 µg given as the fourth dose in BNT162b2-experienced participants >55 years of age. Each primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis ($H_0$) is

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1) \text{ vs } H_1: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$$

where ln(1) corresponds to 1-fold superiority criterion and

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 (30 µg or 60 µg) given as the fourth dose;

  - $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron-neutralizing titers measured 1 month after 1 dose of BNT162b2 at 30 µg given as the fourth dose (Group 1).

- The second null hypothesis ($H_0$) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - $p_1$ is the percentage of participants with seroresponse to Omicron strain at 1 month after 1 dose of BNT162b2 OMI or bivalent BNT162b2 and BNT162b2 OMI given as a fourth dose;

  - $p_2$ is the percentage of participants with seroresponse to Omicron strain at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose (Group 1).

Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

Superiority will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 1; noninferiority based on seroresponse will be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

The secondary objectives of "super" superiority will be evaluated using a 1.5-fold margin for GMR. "Super" superiority for GMR will be established if the lower limit of the 2-sided 95% CI for the GMR is greater than 1.5.

**Noninferiority of Reference Strain Immune Responses**

The noninferiority immunogenicity objectives on reference strain immune responses are to assess the noninferiority of the reference strain immune response induced by a dose of bivalent BNT162b2 and BNT162b2 (30 µg or 60 µg) relative to the reference strain immune response elicited by a dose of BNT162b2 at 30 µg given as the fourth dose in BNT162b2-experienced participants >55 years of age. Each noninferiority objective will be evaluated by the following 2 hypotheses:

- The null hypothesis ($H_0$) is

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

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

  - $\ln(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as the fourth dose (Group 5 or 6);

- $\ln(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured 1 month after 1 dose of BNT162b2 at 30 µg given as the fourth dose (Group 1).

Noninferiority based on GMR will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8.

### 5.1.2. Multiplicity Adjustment

The primary and secondary immunogenicity objectives for participants >55 years of age will be assessed using the expanded-enrollment cohort.

The primary and secondary immunogenicity objectives for participants >55 years of age will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G4vG1A (OMI-60) → G6vG1A (Bivalent-60) → G5vG1A (Bivalent-30) →
- Noninferiority in GMR for reference strain response: G6vG1B (Bivalent-60 ) → G5vG1B (Bivalent-30) →
- "Super" superiority in GMR for Omicron response: G4vG1B (OMI-60) →G6vG1C (Bivalent-60) → G5vG1C (Bivalent-30) →
- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G3vG1A (OMI-30) → G3vG1B (OMI-30)

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference will be assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled.

The immunogenicity objectives for participants 18 to 55 years of age are descriptive only; therefore, no multiplicity adjustment is applied.

## 5.2. General Methods

All analyses will be performed separately for each age group (18 to 55 years of age, >55 years of age) unless otherwise specified.

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

### 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]

As a sensitivity analysis approach, the difference in seroresponse rate between 2 vaccine groups and the associated 95% CI will be calculated using the stratified Miettinen and Nurminen method adjusting for the corresponding baseline assay result category strata (<median, ≥median).

### 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 Mean Titers

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 Between-Group Comparison

Unadjusted

For comparison of immune response between 2 vaccine groups, the GMR will be calculated as the mean of the difference of logarithmically transformed assay results between the two groups and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

Model-Based

As a sensitivity analysis approach, the GMR and associated 95% CI will be calculated by exponentiating the difference in least-squares means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of baseline assay results (log scale) and vaccine group.

#### 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 study 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 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

- Estimands: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: 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 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 for dose 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 for dose 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

- Estimands: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 7 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: 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. Confirmed e-diary errors will be excluded from the analysis.

- 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 for sentinel and expanded cohort.
- 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

Related AEs, severe AEs, and 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.

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

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 for both sentinel and expanded cohorts.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the study vaccination through 6 months after the study vaccination will be provided for each vaccine group.
- Supplemental Analyses
- SAEs from the study vaccination through 7 days after the study vaccination will be summarized similarly for the IRC and at corresponding planned analysis timing described in Section 7.3.

#### 6.1.1.5. Troponin I Level

##### 6.1.1.5.1. Main Analysis

- Estimand: Percentage of participants with elevated troponin I level.
- Analysis set: Safety population of sentinel 18- to 55-year age cohort (Section 4).
- Analysis time point: Before the study vaccination and 3 days after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed (Section 5.3).
- Reporting results: Counts, percentages of participants with elevated troponin I level before study vaccination and 3 days after the study vaccination, and the associated Clopper-Pearson 95% CIs.

### 6.1.2. Primary Immunogenicity Endpoints

#### 6.1.2.1. Main Analysis

Each primary immunogenicity objective involves 2 hypotheses based on GMR and difference of seroresponse rates.

**For Superiority Hypothesis Test based on GMR of Omicron-Neutralizing Titer on G3vG1A, G4vG1A, G5vG1A, and G6vG1A:**

- Estimands: GMRs of Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI 30 µg (Group 3), BNT162b2 OMI 60 µg (Group 4), bivalent BNT162b2 and BNT162b2 OMI 30 µg (Group 5), or bivalent BNT162b2 and BNT162b2 OMI 60 µg (Group 6) to those at 1 month after 1 dose of BNT162b2 30 µg given as a fourth dose (Group 1)
- Analysis set: Evaluable immunogenicity population, and all-available immunogenicity population (as applicable) of >55 years of age (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: 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. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.

- Reporting results: GMR and the associated 2-sided 95% CI will be provided.

**For Noninferiority Hypothesis Tests on Seroresponse Rate of G3vG1A, G4vG1A, G5vG1A, and G6vG1A:**

- Estimands: The difference in percentages of participants with seroresponse to Omicron strain at 1 month after study vaccination.
- Analysis set: Evaluable immunogenicity population and all-available immunogenicity population (as applicable) of >55 years of age (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: The percentages of participants with seroresponse for each group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method (Section 5.2.1).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.
- Reporting results: Counts, percentages of participants with seroresponse in each group, the difference in percentages between groups, and the associated 2-sided 95% CI will be provided.

#### 6.1.2.2. Sensitivity Analysis

GMRs and the associated 2-sided 95% CI, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs may be estimated using the sensitivity analysis approach specified in Section 5.2 (regression model-based estimate for GMR and stratified Miettinen and Nurminen estimate for difference in seroresponse rate).

### 6.1.3. Secondary Analysis

#### 6.1.3.1. Main Analysis

**For Noninferiority Hypothesis Tests of Reference-Strain–Neutralizing Titers on G5vG1B and G6vG1B:**

- Estimands: GMRs of reference-strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI 30 µg (Group 5), or bivalent BNT162b2 and BNT162b2 OMI 60 µg (Group 6) to those at 1 month after 1 dose of BNT162b2 30 µg given as a fourth dose (Group 1).

- Analysis set: Evaluable immunogenicity population, and all-available immunogenicity population (as applicable) >55 years of age (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: 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. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.
- Reporting results: GMR and the associated 2-sided 95% CI will be provided.

**For "Super" Superiority Hypothesis Tests of Seroresponse Rate on G3vG1B, G4vG1B, G5vG1C, and G6vG1C:**

- Estimands: GMRs of Omicron-neutralizing titers at 1 month 1 dose of BNT162b2 OMI 30 µg (Group 3), BNT162b2 OMI 60 µg (Group 4), bivalent BNT162b2 and BNT162b2 OMI 30 µg (Group 5), or bivalent BNT162b2 and BNT162b2 OMI 60 µg (Group 6) to those at 1 month after 1 dose of BNT162b2 30 µg given as a fourth dose (Group 1) after the study vaccination
- Analysis set: Evaluable immunogenicity population, and all-available immunogenicity population (as applicable) of >55 years of age (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: 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. Only participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection will be included in the analysis.
- Reporting results: GMR and the associated 2-sided 95% CI will be provided.

#### 6.1.3.2. Sensitivity Analysis

GMRs and the associated 2-sided 95% CI, and the difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs may be estimated using the sensitivity analysis approach specified in Section 5.2 (regression model-based estimate for GMR and stratified Miettinen and Nurminen estimate for difference in seroresponse rate).

### 6.1.4. Exploratory Immunogenicity Endpoints

#### 6.1.4.1. SARS-CoV-2 Omicron- or Reference-Strain–Neutralizing Titers

- 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- and reference-strain–neutralizing titers from before the study vaccination to subsequent time points for each vaccine group.

  3) Percentages of participants with seroresponse to Omicron or reference strain at each time point.

- Analysis set: Evaluable immunogenicity population (Section 4).

- Analysis time point: Baseline and each subsequent time point after vaccination.

- 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 5.2.2.1. The GMFRs and the associated 2-sided 95% CIs from baseline 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% CIs will be provided for each vaccine group (Section 5.2.1).

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

- Reporting results: GMTs at each time point and GMFRs of SARS-CoV-2 Omicron- or reference-strain–neutralizing titers from baseline (before the first study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for each 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.

- Supportive analyses: GMRs and the differences in percentages of participants with seroresponse between certain vaccine groups of interest (e.g. each vaccine group in the 18-55 year-old group vs the bivalent BNT162b2 30 µg group in the >55 year-old group) may be calculated along with the associated 2-sided 95% CIs.

**Figures:**

- Empirical RCDCs will be provided for SARS-CoV-2 Omicron-strain and SARS-CoV-2 reference-strain–neutralizing titers at each time point for each vaccine group for sentinel and expanded cohort respectively.

- Bar charts of GMT and 95% CI of SARS-CoV-2 Omicron-strain and SARS-CoV-2 reference-strain–neutralizing titers will be plotted for each vaccine group for sentinel and expanded cohort, respectively.

#### 6.1.4.2. SARS-CoV-2–Neutralizing Titers for the Reference Strain and VOCs for Sentinel Cohorts

- Estimands:

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

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

  3) Percentages of participants with seroresponse to reference strain and VOCs at each time point for each vaccine group.

- Analysis set: Evaluable immunogenicity population from sentinel cohorts.

- Analysis methodology: GMTs, GMFRs, and percentages of participants with seroresponse for sentinel cohorts, along with the associated 95% CIs, will be calculated using same method as described in Section 6.1.4.1.

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

- Estimands: GMTs for any VOCs not already specified, after any dose of BNT162b2 OMI or BNT162b2.

- Analyses: GMTs of SARS-CoV-2 VOC–neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each group. GMFRs (Section 5.2.2.2) of SARS-CoV-2 VOC–neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.

#### 6.1.4.4. COVID-19 Cases

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

#### 6.1.4.5. 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 the subset of participants with PBMC samples collected in each vaccine group.

### 6.2. Subset Analyses

Subgroup analyses by sex, race, ethnicity, and baseline SARS-CoV-2 status will be performed on all primary safety and immunogenicity endpoints (as supplemental analyses). Subgroup analyses of immunogenicity endpoints by timing of previous dose of BNT162b2 may also be performed.

### 6.3. Baseline and Other Summaries and Analyses

#### 6.3.1. Baseline Summaries

#### 6.3.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination, sex, race, ethnicity, baseline SARS-CoV-2 status, and classification of BMI will be summarized using descriptive statistics for each vaccine group 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.

#### 6.3.1.2. 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.

#### 6.3.2. Study Conduct and Participant Disposition

#### 6.3.2.1. 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, 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). 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.

#### 6.3.2.2. 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.

#### 6.3.2.3. 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.

### 6.3.3. Study Intervention Exposure

#### 6.3.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving the study intervention 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 the study vaccination will be presented.

#### 6.3.3.2. 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.

## 6.4. Safety Summaries and Analyses

### 6.4.1. 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. Analyses Timing

Statistical analyses will be carried out when the following data are available for each age group:

- Safety data through 1 month after study vaccination for each group in sentinel cohorts.
- Immunogenicity data through 1 month after study vaccination for each group in sentinel cohorts.
- Safety data through 1 month after study vaccination for each group in expanded-enrollment cohort.
- Immunogenicity data through 1 month after study vaccination for each group in expanded-enrollment cohort.
- Complete safety and immunogenicity analysis approximately 6 months after study vaccination for each group in sentinel or expanded-enrollment cohorts.

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.

# 9. APPENDICES

## Appendix 1. List of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ATC | Anatomic Therapeutic Chemical |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| 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 Web-based response |
| LLOQ | lower limit of quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | not applicable |
| OMI | Omicron |
| PA | protocol amendment |
| PBMC | peripheral blood mononuclear cell |
| 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

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