Protocol C4591044

AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 1/2/3 STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162B RNA-BASED VACCINE CANDIDATES IN COVID-19 VACCINE–EXPERIENCED HEALTHY INDIVIDUALS

Statistical Analysis Plan
(SAP)

Version: 4

Date: 03 Aug 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol	Rationale	Specific Changes
1 12 Jul 2022	Original 24 Jun 2022	N/A	N/A
2 15 Sep 2022	Protocol amendment 1 (PA1), 27 Jul 2022 Protocol amendment 2 (PA2), 24 Aug 2022	1. Adjusted the study design to include pediatric participants; removed the blinding level and changed Phase 2 to Phase 2/3 2. Added primary safety and immunogenicity objectives, endpoints, and estimands for each cohort 3. Added secondary objectives, endpoints, and estimands 4. Added exploratory objectives, endpoints, and estimands for each cohort 5. Changed the reporting of COVID-19 symptoms in the event of a positive COVID-19 test result. Included information about participants taking medications intended to treat COVID-19 6. Made adjustments to the general statistical methods 7. Adjusted analyses timing in accordance with regulatory agency's feedback 8. Deleted "vaccine" when in front of "group;" added "assigned" with "randomized"; removed "Omicron sublineages"	1. Changed the title, Section 2.3, Section 3.1.1.5, Section 7, and Figure 1. 2. Changed Section 2.2, Section 3.1.1, Section 3.1.2, Section 6.1.1, and Section 6.1.2 3. Changed Section 2.2 and Section 3.2; added Section 6.2 4. Changed Section 2.2, Section 3.3, and Section 6.3 5. Changed Section 3.1.1.2 and Section 3.4.3 6. Added Section 5.1 and Section 5.2.4; changed Section 5.2.1 7. Changed Section 7.3 8. Changed throughout the document

Table 1. Summary of Changes

Version/ Date	Associated Protocol	Rationale	Specific Changes
3 14 Nov 2022	N/A	Per CBER request, clarify how to calculate median baseline titer level for the analysis of the differences in seroresponse rates using the Miettinen and Nurminen method stratified by the baseline titer category (<median or ≥median)	Changed Section 5.2.1 and Section 6.1.2.2.1
4 03 Aug 2023	Protocol amendment 6 (PA6), 27 Jul 2023	1. Updates in the protocol title 2. Added design, objective, and analysis for Cohort 4 3. Split the analysis time points for primary/secondary immunogenicity objectives and exploratory objectives 4. Clarified consolidation of reactogenicity events recorded on the AE CRF with e-diary data for reactogenicity summary 5. To permit analyses to inform product development and/or for program-level decisions per PACL dated 15 Feb 2023 6. Made other minor modifications to align with the revisions outlined in protocol amendment 6.	• Updates in the protocol title • Section 2.2, Section 2.3, Section 3.1.2, Section 3.2, Section 3.3, Section 5, Section 6.1.2, Section 6.3.1, Section 6.3.4, Section 6.4 • Section 3.1.1, Section 6.1.1 • Section 7.3

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591044. 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 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). In general, completely missing reactogenicity data (ie, all 7 days of collection are missing) will not be imputed. For the partially missed reactogenicity data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.

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

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Cohort 4[a]: To describe the safety and tolerability profile of BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to 1 month after BNT162b2, given	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
compared to after BNT162b2 30 µg[d] given as a second booster dose to BNT162b2-experienced participants >55 years of age	as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[e] or 60 µg[e] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55,[e] and >55[e] years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Cohort 4[a]: To describe the immune response to BNT162b2 Bivalent 30 µg, BNT162b5 Bivalent 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccination for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[d] given as a second booster dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined[f] and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[d] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age	In participants complying with the key protocol criteria (evaluable participants): • GMT at baseline and 1 month after the study vaccinaton for each strain-specific neutralizing titer • GMFR from before the study vaccination to 1 month after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at 1 month after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Exploratory		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): At baseline and 7 days, 1 month, 3 months, and 6 months after study vaccination • GMT each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
	point after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point after the study vaccination for each strain-specific neutralizing titer	
Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined,[f] Cohort 2/Group 4 + Cohort 3/Group 2 combined,[f] Cohort 2/Group 3, and Cohort 2/Group 5: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg compared to BNT162b2 30 µg[f] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age	In participants complying with the key protocol criteria (evaluable participants): At baseline and 1 month, 3 months, and 6 months after the study vaccination • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 4[a]: To describe the immune response to BNT162b2 Bivalent 30 µg, BNT162b5 30 µg, BNT162b6 Bivalent 30 µg, BNT162b7 Bivalent 30 µg, and BNT162b7 Monovalent 30 µg given to mRNA COVID-19 vaccine–experienced participants 18 through 55 years of age	In participants complying with the key protocol criteria (evaluable participants): At baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point after the study vaccination for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point after the study vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[g] and at the convalescent visit		• SARS-CoV-2–neutralizing titers previously specified for the respective cohorts

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4: To describe the immune response to other emerging variants (under monitoring, of interest, and/or of concern)		• SARS-CoV-2–neutralizing titers for other variants (under monitoring, of interest, and/or of concern) not already specified
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[c] and Omicron in a subset of participants with PBMC samples collected		

a. The Cohort 4 bivalent vaccines target the SARS-CoV-2 Original strain and the Omicron variant (BA.4/BA.5 sublineage). The Cohort 4 monovalent vaccine targets the Omicron variant (BA.4/BA.5 sublineage).
b. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
c. Reference strain is also referred to as the Original, Wild Type, or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
d. The participants >55 years of age from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
e. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from the C4591031 Substudy E expanded cohort who received Bivalent BNT162b2 (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.
f. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from C4591044 Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg and from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be selected for this objective. The subset selected will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status, whenever feasible.
g. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

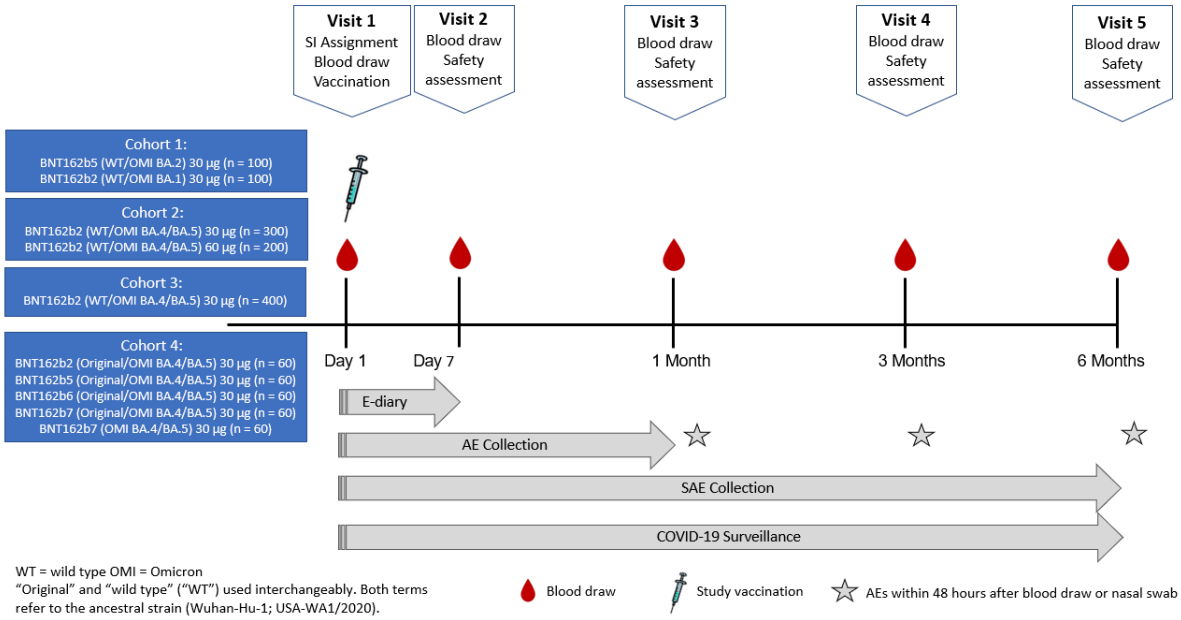
2.3. Study Design

This study is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent and monovalent vaccines. The study duration for each participant will be approximately 6 months. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan. Refer to the Schema in Figure 1.

Based on review of safety or immunogenicity data of any study intervention group, at Pfizer's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed, and study visits or other procedures may be discontinued.

An EDMC will review cumulative unblinded data throughout the study.

Figure 1. Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Safety Endpoints

The primary safety endpoints for all analysis groups are as follows:

- Local reactions for up to 7 days after the study vaccination
- Systemic events for up to 7 days after the study vaccination
- AEs from vaccination through 1 month after the study vaccination
- SAEs from vaccination through 6 months after the study vaccination

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after the study vaccination, where Day 1 is the day of the study vaccination. The e-diary entries from the participant and unplanned clinical assessments within 7 days after vaccination will be the primary data sources for these events. In addition, any events recorded on the AE CRF that are considered local reactions within 7 days after vaccination will be consolidated with e-diary data and included in the reactogenicity report. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 3 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of the study vaccination.

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

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

Note: Completely missing 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 formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 4.

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

Table 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 reaction should be reported as an AE in the CRF 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 Pfizer.

For each local reaction reported after the study vaccination, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of the study vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after administration (Day 1 through Day 7) among severity grades reported for that local reaction.

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

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive (last day of reaction − first day of reaction + 1). Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasts 7 days or less, or the day the reaction ends if it persists beyond the end of the reactogenicity e-diary period following the study vaccination (the latter will be collected on the CRF). If there is no known date when

the reaction ended, then duration will be missing (unknown). Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if participants report change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

3.1.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after the study vaccination. The e-diary entries from the participant and unplanned clinical assessments within 7 days after vaccination will be the primary data sources for these events. In addition, any events recorded on the AE CRF that are considered systemic events starting within 7 days after vaccination will be consolidated with e-diary data and included in the reactogenicity report. The derivations for systemic events will be handled similar to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5 and recorded in the e-diary. For events recorded in the AE CRF that are considered systemic events and consolidated with e-diary data, the severity will be based on the AE intensity grade recorded in the CRF.

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

Table 5. Systemic Event Grading Scale

	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

Table 5. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
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 a positive test result, the symptoms should be recorded in the potential COVID-19 illness CRFs (with potential COVID-19 illness visit completed) rather than as systemic events in the reactogenicity e-diary (refer to the protocol, Sections 8.10.7 and 8.10.8).

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

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C (<95.0°F) and >42.0°C (>107.6°F) will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 6 below.

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. Fevers >40.0°C (>104.0°F) will be collected as an AE on the CRF and assessed by the investigator using the AE intensity grading scale (Protocol, Section 10.3.3). If a fever is reported in the AE CRF within 7 days after vaccination and no temperature was captured in the CRF, the fever will be included in the reactogenicity summary with "unknown" for temperature range.

Table 6. Scale for Fever

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

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

3.1.1.3. Antipyretic/Analgesic Medication

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

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

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

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 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 SOC and PT.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol).

3.1.1.5. Serious Adverse Events

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

3.1.2. Primary Immunogenicity Endpoints

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

Cohort 1:

- SARS-CoV-2 Omicron (BA.2)–neutralizing titers at baseline and 1 month after the study vaccination
- SARS-CoV-2 Omicron (BA.1)–neutralizing titers at baseline and 1 month after the study vaccination
- SARS-CoV-2 reference-strain–neutralizing titers at baseline and 1 month after the study vaccination

Cohort 2:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at baseline and 1 month after the study vaccination
- SARS-CoV-2 Omicron (BA.1)–neutralizing titers at baseline and 1 month after the study vaccination
- SARS-CoV-2 reference-strain–neutralizing titers at baseline and 1 month after the study vaccination

Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined:

In participants with and without evidence of SARS-CoV-2 infection:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at 1 month after the study vaccination

Cohort 4:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at baseline and 1 month after the study vaccination
- SARS-CoV-2 reference-strain–neutralizing titers at baseline and 1 month after the study vaccination

3.2. Secondary Endpoint(s)

Cohort 2/Group 4 + Cohort 3/Group 2 combined (>55-year age group):

In participants with and without evidence of SARS-CoV-2 infection:

- SARS-CoV-2 reference-strain–neutralizing titers at 1 month after the study vaccination

Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined:

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at 1 month after the study vaccination
- SARS-CoV-2 reference-strain–neutralizing titers at 1 month after the study vaccination

3.3. Exploratory Endpoint(s)

Cohort 1:

- SARS-CoV-2 Omicron (BA.2)–neutralizing titers at baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination
- SARS-CoV-2 Omicron (BA.1)–neutralizing titers at baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination

- SARS-CoV-2 reference-strain–neutralizing titers at baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination

Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined, Cohort 2/Group 4 + Cohort 3/Group 2 combined, Cohort 2/Group 3, and Cohort 2/Group 5:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at baseline and 1 month, 3 months, and 6 months after the study vaccination
- SARS-CoV-2 reference-strain–neutralizing titers at baseline and 1 month, 3 months, and 6 months after the study vaccination

Cohort 4:

- SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers at baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination
- SARS-CoV-2 reference-strain–neutralizing titers at baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination

Cohort 1, Cohort 2 + Cohort 3 combined, and Cohort 4:

- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Strain sequencing of COVID-19 cases
- SARS-CoV-2–neutralizing titers previously specified for the respective cohorts at the COVID-19 illness visit and the convalescent visit
- SARS-CoV-2–neutralizing titers for other emerging variants (under monitoring, of interest, and/or of concern) not already specified

Cohort 2:

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

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 20th birthday, the participant is considered to be 19 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, a physical examination will be performed. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

3.4.2. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all the items on the e-diary for all 7 days after vaccination, the e-diary will be considered not transmitted.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Prohibited medications listed in the protocol, Section 6.9.1, will be recorded in the concomitant medication CRF (with the exception of prophylactic antipyretics and other pain medication to prevent symptoms) to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit will be recorded in the nonstudy vaccination CRF.

- All prior COVID-19 vaccinations will be recorded in the prior COVID-19 vaccination CRF.

- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

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

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs 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.

Population	Description
Screened	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized/assigned, have at least 1 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 (mITT)	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.

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

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized/assigned. Missing serology data will not be imputed.

5. GENERAL METHODOLOGY AND CONVENTIONS

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

Cohort 1, Cohort 2, and Cohort 4: To facilitate rapid review of data in real time, the majority of Pfizer/BioNTech staff will be unblinded to the study intervention allocation.

Cohort 3: Given the single study intervention arm, both groups are unblinded to the majority of Pfizer staff involved in the conduct of the study.

All Cohorts: 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 6.4. The timing for statistical analysis is specified in Section 7.3.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

Cohort 1, Cohort 2, and Cohort 4: For objectives evaluated separately within Cohort 1, Cohort 2, and Cohort 4, there is no formal hypothesis testing. All statistical analyses will be descriptive.

Cohort 2 and Cohort 3 combined:

Superiority and Noninferiority of Anti-Omicron Immune Responses

For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):

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

BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti-Omicron immune response elicited by BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E.

The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

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

where ln(1) corresponds to a 1-fold margin for superiority and

  - Ln(μ_1) is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - Ln(μ_2) is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 given as a second booster dose in the >55-year age group from C4591031 Substudy E.

- The second null hypothesis (H_0) is

$$H_0: p_1 - p_2 \leq -0.05 \text{ vs } H_1: p_1 - p_2 > -0.05$$

where -5% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - p_2 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 given as a second booster dose in the >55-year age group from C4591031 Substudy E.

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

Superiority based on GMR 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%.

For the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined)**:**

The primary immunogenicity objective is to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1) relative to the anti-Omicron immune response elicited by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2). The primary objective will be evaluated by the following 2 hypotheses:

- The first null hypothesis (H_0) is

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

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

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1);

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 Omicron (sublineage BA.4/BA.5)–neutralizing titer measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2).

- The second null hypothesis (H_0) is

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

where -10% is the noninferiority margin for seroresponse and

  - p_1 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the 18- to 55-year age group (Cohort 2/Group 2+ Cohort 3/Group 1);

  - p_2 is the percentage of participants with seroresponse to the Omicron strain (sublineage BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2).

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

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

Noninferiority of Anti–Reference-Strain Immune Responses

The secondary immunogenicity objective is to assess the noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti–reference strain immune response elicited by BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E. The noninferiority objective will be evaluated by the following hypothesis:

- 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

  - $\text{Ln}(\mu_1)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose in the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2);

  - $\text{Ln}(\mu_2)$ is the natural log of the geometric mean of SARS-CoV-2 reference-strain–neutralizing titers measured at 1 month after BNT162b2 given as a second booster dose in the >55-year age group from C4591031 Substudy E.

Noninferiority based on the 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

Cohort 1, Cohort 2, and Cohort 4: No multiplicity adjustment is needed for objectives evaluated separately within Cohort 1, Cohort 2, and Cohort 4, as there are no statistical hypotheses.

Cohort 2 + Cohort 3 combined:

The primary and secondary objectives will be evaluated sequentially using a 1-sided alpha of 0.025. The primary objective for the >55-year age group (with respect to the anti-Omicron BA.4/BA.5 immune response) will be evaluated first, followed by the secondary objective of the GMR for the >55-year age group (with respect to the anti–reference-strain immune response), and then the primary objective for the 18- to 55-year age group (with respect to the anti-Omicron BA.4/BA.5 immune response). The later objective will be evaluated only if the previous objective is met.

The primary objectives involve 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error is fully controlled.

5.2. General Methods

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

5.2.1. Analyses for Binary Endpoints

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

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

The primary approach to calculate the difference in seroresponse rate between 2 groups and the associated 95% CI will be based on Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers will be calculated based on the pooled data in 2 comparator groups.

5.2.2. Analyses for Continuous Endpoints

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

5.2.3. Geometric Means

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

5.2.4. Geometric Mean Ratios

Model-Based GMR:

As the primary approach, the GMR and associated 95% CI will be calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes terms for baseline neutralizing titer and comparison group.

Unadjusted GMR:

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.5. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean.
The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.6. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the study vaccination date(s) from the same participant, following the Pfizer standard for handling an incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoints

All primary safety endpoints will be summarized by age group (as applicable) and vaccine group for Cohort 1, Cohort 2, Cohort 2 and Cohort 3 combined (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined), and Cohort 4.

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 or unplanned clinical assessment data and without reactogenicity data reported in the AE CRF throughout the 7 days after vaccination will be excluded from the analysis; completely missing reactogenicity data (ie, all 7 days of collection are missing) will not be imputed. For the partially missed reactogenicity data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on the missing days.
- Reporting results: Descriptive statistics for each and any local reaction after the study vaccination in each 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 Analysis

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population as above, and appropriate analysis methodology and reporting results:

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

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by group.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after the study vaccination will be plotted by 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 or unplanned clinical assessment data and without reactogencity events reported in the AE CRF throughout the 7 days after vaccination will be excluded from the analysis; completely missing reactogenicity data (ie, all 7 days of collection are missing) will not be imputed. For the partially missed reactogenicity data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced.

- Reporting results: Descriptive statistics for each systemic event after the study vaccination in each 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 Analysis

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions:

- Duration of each systemic event after the study vaccination.

- Onset day of each systemic event after the study vaccination.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum by 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 group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the study vaccination through 1 month after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 1 month after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1 and Section 3.1.1.4).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of AEs within 1 month after the study vaccination will be provided for each group.

6.1.1.3.2. Supplemental Analysis

Related AEs, severe AEs, immediate AEs (within the first 30 minutes after the study vaccination), and AESIs (defined in Section 8.4.8 of the protocol) will also be summarized by group.

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

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from the study vaccination through 6 months after the study vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the study vaccination through 6 months after the study vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the study vaccination through 6 months after the study vaccination will be provided for each group.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Cohort 1, Cohort 2, and Cohort 4

6.1.2.1.1. Main Analysis

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- Estimands (Cohort 1):
  - GMTs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers at baseline and 1 month after the study vaccination for each vaccine group
  - GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers from before the study vaccination to 1 month after the study vaccination for each vaccine group
  - Percentages of participants with seroresponse to Omicron strain (sublineages BA.1 and BA.2) and reference-strain–neutralizing titers at 1 month after the study vaccination
- Estimands (Cohort 2):
  - GMTs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.4/BA.5) and reference-strain–neutralizing titers at baseline and 1 month after the study vaccination for each group (Cohort 2/Group 1 to Group 5 and comparator groups from C4591031 Substudy E, Table 7)
  - GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to 1 month after the study vaccination for each group (Cohort 2/Group 1 to Group 5 and comparator groups from C4591031 Substudy E, Table 7)
  - Percentages of participants with seroresponse to Omicron strain (sublineages BA.1 and BA.4/BA.5) and reference-strain–neutralizing titers at 1 month after the study vaccination for each group (Cohort 2/Group 1 to Group 5 and comparator groups from C4591031 Substudy E, Table 7)
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- 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 5.2.3. 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 5.2.5. The percentages of participants with seroresponse at each time point and the associated

Clopper-Pearson 95% CIs will be provided for each group (Section 5.2.1). Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

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

- Reporting results: GMTs at baseline and 1 month after the study vaccination and GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.1 and BA.2 for Cohort 1; sublineages BA.1 and BA.4/BA.5 for Cohort 2) and reference-strain–neutralizing titers from baseline (before the study vaccination received in this study) to 1 month after vaccination, along with the associated 2-sided 95% CIs, will be provided for each group for participants without evidence of SARS-CoV-2 infection and for participants with and without evidence of SARS-CoV-2 infection. The percentages of participants with seroresponse at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided for each group for participants without evidence of SARS-CoV-2 infection and for participants with and without evidence of SARS-CoV-2 infection.

Table 7. Outline of Primary Objectives Groups (Cohort 2)

	C4591044 Cohort 2	C4591031 Substudy E
Study Intervention	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	Bivalent BNT162b2 (WT/OMI BA.1)
Group	Group 1	
Age (years)	12-17	
Dosage level	30 µg	
Group	Group 2	Group 8
Age (years)	18-55	18-55
Dosage level	30 µg	30 µg
Group	Group 3	Group 7
Age (years)	18-55	18-55
Dosage level	60 µg	60 µg
Group	Group 4	Group 5
Age (years)	>55	>55
Dosage level	30 µg	30 µg
Group	Group 5	Group 6
Age (years)	>55	>55
Dosage level	60 µg	60 µg

- Estimands (Cohort 4):
    - GMTs of SARS-CoV-2 Omicron strain (sublineages BA.4/BA.5) and reference-strain–neutralizing titers at baseline and 1 month after the study vaccination for each vaccine group
    - GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to 1 month after the study vaccination for each vaccine group
    - Percentages of participants with seroresponse to Omicron strain (sublineages BA.4/BA.5) and reference-strain–neutralizing titers at 1 month after the study vaccination for each vaccine group
- Analysis set, analysis methodology, intercurrent events, and missing data are the same as described above for Cohort 1 and Cohort 2.
- Reporting results: In participants with and without evidence of SARS-CoV-2 infection, GMTs and GMFRs of SARS-CoV-2 Omicron (sublineages BA.4/BA.5)–neutralizing and reference-strain–neutralizing titers, and percentages of participants with seroresponse to SARS-CoV-2 Omicron (sublineages BA.4/BA.5) and reference strain, along with the associated 95% CIs, will be provided for each vaccine group, overall and by baseline SARS-CoV-2 infection status.

6.1.2.2. Cohort 2 and Cohort 3 Combined

6.1.2.2.1. Main Analysis

In participants with and without evidence of SARS-CoV-2 infection:

For Superiority Hypothesis Test

- Estimands: GMRs of Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined to 1 month after BNT162b2 given as a second booster dose for C4591031 Substudy E Group 1.
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs along with the model-based LS GMT and associated 2-sided 95% CIs will be calculated using the linear regression model that includes terms for baseline neutralizing titer and comparison group. Statistical method is described in Section 5.2.4.

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

- Reporting results: The LS GMT and associated 95% CIs from each comparison group, as well as the model-based GMR with their associated 95% CIs, will be summarized.

For Noninferiority Hypothesis Test

- Estimands:

    - The difference in percentages of participants with seroresponse to the Omicron strain (BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined to 1 month after BNT162b2 given as a second booster dose for C4591031 Substudy E Group 1

    - GMRs of Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 2 + Cohort 3/Group 1 combined to 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined

    - The difference in percentages of participants with seroresponse to the Omicron strain (BA.4/BA.5) at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 2 + Cohort 3/Group 1 combined to 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined

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

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs along with the model-based LS GMTs and associated 2-sided 95% CIs for each group will be calculated using the linear regression model that includes terms for baseline neutralizing titer and comparison group. Statistical methods described in Section 5.2.4.
  The percentages of participants with seroresponse and the associated Clopper-Pearson 95% CIs for each comparison group will be provided. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers will be calculated based on the pooled data in 2 comparator groups. Statistical methods are described in Section 5.2.1.

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

- Reporting results: The LS GMTs and associated 95% CIs from each comparison group, as well as the model-based GMR with their associated 95% CIs, will be summarized. The number/percentages of participants with seroresponse for each comparison group and the corresponding 95% CIs, along with the difference in percentages of participants with seroresponse between the 2 comparison groups and the associated 2-sided 95% CIs, will be provided.

6.1.2.2.2. Sensitivity Analysis

To support the interpretation of the primary analysis, the unadjusted GMTs and 95% CIs will be provided for each comparison group, both before the study vaccination and 1 month after vaccination. The unadjusted GMR and 95% CIs will also be calculated based on the Student t distribution. Statistical methods are described in Section 5.2.4.

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

Supportive analyses in participants without evidence of SARS-CoV-2 infection may also be performed.

6.2. Secondary Endpoint(s)

6.2.1. Secondary Immunogenicity Endpoints

6.2.1.1. Main Analysis

For Noninferiority Hypothesis Test

For the >55-year age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):
In participants with and without evidence of SARS-CoV-2 infection:

- Estimands: GMRs of reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for Cohort 2/Group 4 + Cohort 3/Group 2 combined to 1 month after BNT162b2 given as a second booster dose for C4591031 Substudy E Group 1.

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

- Analysis time point: 1 Month after vaccination.

- Analysis methodology: Model-based GMRs and the associated 2-sided 95% CIs along with the model-based LS GMTs and associated 2-sided 95% CIs for each group will be calculated using the linear regression model that includes terms for baseline neutralizing titer and comparison group. Statistical method described in Section 5.2.4.

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

- Reporting results: The LS GMTs and associated 95% CIs from each comparison group, as well as the model-based GMR with the associated 95% CI, will be summarized.

- Supportive Analysis: As supportive analysis, the unadjusted GMTs and 95% CIs before study vaccination and 1 month after vaccination will be provided for each comparison group. The unadjusted GMR and 95% CIs will also be calculated based on the t distribution. Statistical methods are described in Section 5.2.4. The same analyses in participants without evidence of SARS-CoV-2 infection may also be performed as supportive.

For Descriptive Summary

For Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined:

In participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection:

- Estimands:
    - GMTs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at baseline and 1 month after the study vaccination for each group (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined)
    - GMFRs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to 1 month after the study vaccination for each group (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined)
    - Percentages of participants with seroresponse to Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at 1 month after the study vaccination for each group (Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined)
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- 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 5.2.3. 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 5.2.5. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each 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 baseline and 1 month after the study vaccination and GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.4/BA.5) and reference-strain–neutralizing titers from baseline to 1 month after the study vaccination, along with the associated 2-sided 95% CIs, will be provided for each group in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection. The percentages of participants with seroresponse at 1 month after the study vaccination and the associated Clopper-Pearson 95% CIs will be provided for each group in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection.

6.3. Exploratory Endpoint(s)

6.3.1. Immunogenicity

For Cohort 1: At baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination

- Estimands:
    - GMTs of SARS-CoV-2 Omicron strain (BA.1 and BA.2) and reference-strain–neutralizing titers at each time point for each group
    - GMFRs of SARS-CoV-2 Omicron strain (BA.1 and BA.2) and reference-strain–neutralizing titers from before the study vaccination to each subsequent time point after the study vaccination for each group
    - Percentages of participants with seroresponse to Omicron strain (BA.1 and BA.2) and reference-strain–neutralizing titers at each time point after the study vaccination for each group

For C4591044 Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined, Cohort 2/Group 4 + Cohort 3/Group 2 combined, Cohort 2/Group 3, Cohort 2/Group 5, and C4591031 Substudy E Group 1: At baseline and 1 month, 3 months, and 6 months after the study vaccination

- Estimands:
  - GMTs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at each time point for each group
  - GMFRs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to each subsequent time point for each group
  - Percentages of participants with seroresponse to Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at each time point following vaccination for each group

  All participants in Cohort 2/Group 1, Cohort 2/Group 3, Cohort 2/Group 5, and a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from C4591044 Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg and from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be selected for this objective.

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

- 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 5.2.3. 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 5.2.5. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each 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 strain (sublineages BA.1 and BA.2 for Cohort 1; sublineages BA.4/BA.5 for Cohort 2/Cohort 3) and reference-strain–neutralizing titers from baseline to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, and the percentages of participants with seroresponse at each time point, along with the associated Clopper-Pearson 95% CIs, will be provided for each group in participants without evidence of SARS-CoV-2 infection and in participants with and without evidence of SARS-CoV-2 infection.

For Cohort 4: At baseline and 7 days, 1 month, 3 months, and 6 months after the study vaccination

- Estimands:
    - GMTs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at each time point for each group
    - GMFRs of SARS-CoV-2 Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers from before the study vaccination to each subsequent time point for each group
    - Percentages of participants with seroresponse to Omicron strain (BA.4/BA.5) and reference-strain–neutralizing titers at each time point following vaccination for each group
- Analysis set, analysis methodology, intercurrent events, and missing data are the same as describe above for Cohort 1 and Cohort 2/Cohort 3.
- Reporting results: In participants with and without evidence of SARS-CoV-2 infection, GMTs at each time point and GMFRs of SARS-CoV-2 Omicron strain (sublineages BA.4/BA.5) and reference-strain–neutralizing titers from baseline to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, and the percentages of participants with seroresponse at each time point, along with the associated Clopper-Pearson 95% CIs, will be provided for each vaccine group, overall and by baseline SARS-CoV-2 infection status.

6.3.2. COVID-19 Cases

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

6.3.3. SARS-CoV-2–Neutralizing Titers Previously Specified for the Respective Cohorts at COVID-19 Illness Visit and Convalescent Visit

SARS-CoV-2–neutralizing titers at the time of a COVID-19 illness visit and at the convalescent visit will be listed for participants with blood sample taken at these visits.

6.3.4. SARS-CoV-2 Neutralizing Titers for Other Emerging Variants (Under Monitoring, of Interest, and/or of Concern) Not Already Specified

- Estimands:
    - GMTs of SARS-CoV-2–neutralizing titers for other emerging variants not already specified at specific time points for each group
    - GMFRs of SARS-CoV-2–neutralizing titers for other emerging variants not already specified from before the study vaccination to subsequent time points for each group

  - Percentages of participants with seroresponse to SARS-CoV-2–neutralizing titers for other emerging variants not already specified at each time point

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

- 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 5.2.3. 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 5.2.5. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for each 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–neutralizing titers for other emerging variants (under investigation, of interest, and/or concern) from baseline (before the study vaccination received in this study) to each subsequent time point after vaccination, along with the associated 2-sided 95% CIs, will be provided for the specific group. The percentages of participants with seroresponse at each time point and the associated Clopper-Pearson 95% CIs will be provided for the specific group.

6.3.5. Cell-Mediated Immune Response

For Cohort 2, the cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron strain (BA.4/BA.5) will be summarized at each time point for the subset of participants with PBMC samples collected in each group.

6.4. Subset Analyses

For each analysis group in Cohort 1, Cohort 2, and Cohort 2/Cohort 3 combined, subgroup analyses based on sex and baseline SARS-CoV-2 status will be performed on all primary immunogenicity endpoints as supplemental analyses and for all primary safety endpoints.

For Cohort 4, subgroup analyses based on number of prior doses (3 doses or 4 doses) and baseline SARS-CoV-2 status may be performed on primary immunogenicity endpoints as supplemental analyses, if the subgroups have reasonable sample size.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination, sex, race, ethnicity, baseline SARS-CoV-2 status, and classification of BMI, will be summarized using descriptive statistics for each group based on the safety population and the evaluable immunogenicity population. Timing and name of all previous doses of COVID-19 vaccinations prior to enrollment will also be summarized for each group.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of participants with at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by group for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

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

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

6.5.2.2. Blood Samples for Assay

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

6.5.2.3. Transmission of E-Diaries

The number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for the study vaccination will be summarized according to the vaccine actually received.

The safety population will be used.

6.5.3. Study Intervention Exposure

6.5.3.1. Vaccination Timing and Administration

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

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

6.5.3.2. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before the study vaccination will be listed. The number and percentage of participants receiving each concomitant vaccine after the study vaccination will be tabulated by group. Prohibited medications will be summarized in a similar way as concomitant vaccines. Listings of concomitant vaccines and prohibited medications will be provided. The safety population will be used.

6.6. Safety Summaries and Analyses

6.6.1. 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. As Cohort 1, Cohort 2, Cohort 3, and Cohort 4 are included in this sponsor open-label Phase 2/3 study, Pfizer may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

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 of Cohort 1, Cohort 2, Cohort 2 + Cohort 3 combined, and Cohort 4:

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

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

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

At the request of regulatory agencies, analyses of 7-day reactogenicity data for Cohort 2 and descriptive summary of 1-month immunogenicity data for a subset of Cohort 2/Group 4 participants and C4591031 Substudy E Group 1 will be performed.

8. REFERENCES

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

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

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BLQ	below limit of quantitation
BMI	body mass index
BNT162b2 Bivalent (WT/OMI BA.1)	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529 sublineage BA.1)
BNT162b2 Bivalent (Original/OMI BA.4/BA.5)*	BNT162b2 Original and BNT162b2 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b2 Bivalent (WT/OMI BA.4/BA.5)*	BNT162b2 Wild Type and BNT162b2 OMICRON (B.1.1.529) sublineage BA.4/BA.5
BNT162b5 Bivalent (Original/OMI BA.4/BA.5)	BNT162b5 Original and BNT162b5 OMICRON (B.1.1.529 sublineage BA.4/BA.5)
BNT162b5 Bivalent (WT/OMI BA.2)	BNT162b5 Wild Type and BNT162b5 OMICRON (B.1.1.529 sublineage BA.2)
BNT162b6 Bivalent (Original/OMI BA.4/BA.5)	BNT162b6 Original and BNT162b6 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b6 RNA-LNP vaccine utilizing modRNA for the P6 S)
BNT162b7 Bivalent (Original/OMI BA.4/BA.5)	BNT162b7 Original and BNT162b7 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b7 RNA-LNP vaccine utilizing modRNA for the P6 S)
BNT162b7 Monovalent (OMI BA.4/BA.5)	BNT162b7 OMICRON (B.1.1.529) sublineage BA.4/BA.5 (BNT162b7 RNA-LNP vaccine utilizing modRNA for the P6 S)
CBER	Center for Biologics Evaluation and Research (United States)
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IRT	interactive response technology
IRC	internal review committee
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LS	least squares

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
OMI	Omicron
P6 S	SARS-CoV-2 full-length, P6 mutant, prefusion spike glycoprotein
P6' S	SARS-CoV-2 full-length, P6 prime mutant, prefusion spike glycoprotein
PA	protocol amendment
PACL	protocol administrative change letter
PBMC	peripheral blood mononuclear cell
PT	preferred term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SI	study intervention
SOC	system organ class
WHO	World Health Organization
WT	wild type

* BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and BNT162b2 Bivalent (Original/OMI BA.4/BA.5) refer to the same vaccine. The terms wild type and original strain are interchangeable.

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Signed By:	Date(GMT)	Signing Capacity
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