Protocol C4591017

A PHASE 3, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MULTIPLE PRODUCTION LOTS AND DOSE LEVELS OF THE VACCINE CANDIDATE BNT162b2 AGAINST COVID-19 IN HEALTHY PARTICIPANTS 12 THROUGH 50 YEARS OF AGE AND THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED COVID-19 VACCINE CANDIDATES AS A BOOSTER DOSE IN HEALTHY PARTICIPANTS 18 THROUGH 50 YEARS OF AGE

Statistical Analysis Plan
(SAP)

Version: 3

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[redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 17 Feb 2021	1 26 Jan 2021	N/A	N/A
2/ 06 May 2021	2 03 May 2021	Protocol amendment 2 and BDR team review	1. Booster study–related information added. 2. Removed "S1-binding IgG" throughout the document, as "full-length S-binding IgG" assay is the chosen assay for this protocol. 3. "Equivalence" is replaced with "similarity" for statistical comparisons. 4. Removed "by day" e-diary figures.
3/ 15 Oct 2021	2 03 May 2021	CCI [redacted]	1. Revised Section 5.1.2 to sequentially evaluate the 3 primary objectives. 2. Revised Section 7 to indicate 2 separate analyses will be performed.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591017. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary and secondary objective are described in Table 2.1 and Table 2.2. The estimands to evaluate the immunogenicity objectives are based on evaluable populations (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

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

Primary Study

Table 2.1 Primary Study – List of Primary and Secondary Objectives, Endpoints, and Estimands

Primary Immunogenicity Objectives – Lot Comparisons	Estimands	Primary Immunogenicity Endpoints
• To demonstrate that the immune responses induced by BNT162b2 are similar across the 3 US lots (Arms 1, 2, and 3) in participants without evidence of SARS CoV-2 infection during the study.	In participants complying with the key protocol criteria (evaluable participants): • GMR from one US lot to another lot (Arm 1/Arm 2, Arm 1/Arm 3, and Arm 2/Arm 3) 1 month after Dose 2	• Full-length S-binding IgG levels
• To demonstrate that the immune response induced by the EU lot (Arm 4) of BNT162b2 is similar to the pooled US lots (Arms 1, 2, and 3) in participants without evidence of SARS-CoV-2 infection during the study.	In participants complying with the key protocol criteria (evaluable participants): • GMR from EU lot (Arm 4) to the pooled US lots (Arm 4/pooled Arms 1, 2, and 3) 1 month after Dose 2	• Full-length S-binding IgG levels
Primary Immunogenicity Objectives – Dose Comparison	**Estimands**	**Primary Immunogenicity Endpoints**
• To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants receiving 20 µg compared to participants receiving the standard 30-µg dose (prepared from the same manufacturing lot) without evidence of SARS-CoV-2 infection during the study.	In participants complying with the key protocol criteria (evaluable participants): • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 dose groups 1 month after Dose 2	• SARS-CoV-2 neutralizing titers
Primary Safety Objectives	**Estimands**	**Primary Safety Endpoints**
• To evaluate the safety of BNT162b2 when administered on a 2-dose schedule in healthy participants 12 through 50 years of age.	In participants receiving at least 1 dose of study intervention from each vaccine group (individual and pooled US lots, EU lot, 20-µg dose), the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs and SAEs from Dose 1 to 1 month after Dose 2	• 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 2.1 Primary Study – List of Primary and Secondary Objectives, Endpoints, and Estimands

Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
• To describe the immune responses induced by different 30-µg dose manufacturing lots of BNT162b2.	In evaluable participants from each vaccine group (individual and pooled US lots, EU lot): • GMCs at baseline (before Dose 1) and 1 month after Dose 2 • GMFR from baseline (before Dose 1) to 1 month after Dose 2	• Full-length S-binding IgG levels
• To describe the immune responses induced by different doses of BNT162b2.	In evaluable participants from each vaccine group (20 µg and 30 µg from the same US lot): • GMTs at baseline (before Dose 1) and 1 month after Dose 2 • GMFR from baseline (before Dose 1) to 1 month after Dose 2	• SARS-CoV-2 neutralizing titers

Note: "US lots" refers to lots of study vaccine containing drug substance manufactured in the United States. "EU lot" refers to the lot of study vaccine containing drug substance manufactured in Europe.

Booster Study

Table 2.2 Booster Study – List of Primary Objectives, Endpoints, and Estimands

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
• To describe the immune responses induced by a third dose of study intervention (either BNT162b2 30 µg or BNT162b2.B.1.351* 30 µg).	In evaluable participants from each vaccine group (either BNT162b2 30 µg or BNT162b2.B.1.351 30 µg): • Geometric mean neutralizing titers at baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3 • Geometric mean IgG concentrations at baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3 • GMFRs from 1 month after Dose 2 to 1 week after and 1 month after Dose 3 and from before Dose 3 to 1 week after and 1 month after Dose 3 • The percentages of participants with seroresponse§ (based on neutralizing titers) to the reference strain at 1	• SARS-CoV-2 reference-strain neutralizing titer† • SARS-CoV-2 B.1.351-strain neutralizing titer†† • Full-length S-binding IgG levels

Table 2.2 Booster Study – List of Primary Objectives, Endpoints, and Estimands

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
	month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3 • The percentages of participants with seroresponse§ (based on neutralizing titers) to the B.1.351 variant strain at 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3	
Primary Safety Objectives	**Estimands**	**Primary Safety Endpoints**
• To evaluate the safety and tolerability profile of a third dose of study intervention (either BNT162b2 30 µg or BNT162b2.B.1.351* 30 µg) administered to participants (18 through 50 years of age) who received two 30-µg doses of BNT162b2, approximately 3 months after Dose 2.	In participants receiving the third dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the booster dose • Systemic events for up to 7 days following the booster dose • AEs and SAEs from the booster dose to 1 month after the booster dose.	• 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

* BNT162.B.1.351 = BNT162b2s01 vaccine encoding for the full-length spike protein of South African–origin variant B.1.351 (formerly BNT162b2$_{SA}$).
† SARS-CoV-2 reference-strain neutralizing titers = neutralizing titers against SARS-CoV-2 USA-WA1/2020 virus.
†† SARS-CoV-2 B.1.351-strain neutralizing titers = neutralizing titers against SARS-CoV-2 virus with B.1.351 spike.
§ Seroresponse is defined as ≥4-fold increase from baseline (before Dose 1) to the specified time point. If the baseline measurement is below LLOQ, a postvaccination measurement of ≥4 × LLOQ is considered a seroresponse.

2.2. Study Design

Primary Study

This is a Phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of 4 manufacturing lots of BNT162b2 as a 30-µg dose and an additional 20-µg dose arm using one of the same manufactured 30-µg lots. BNT162b2 is an RNA-based COVID-19 vaccine, administered on a 2-dose schedule in healthy participants 12 through 50 years of age. The study will be conducted in the United States.

Participants will be randomized to 1 of 5 arms in a 2:2:2:1:2 ratio (Arm 1: Arm 2: Arm 3: Arm 4: Arm 5), where Arms 1, 2, and 3 contain US-manufactured drug substance for 30-µg dosing; Arm 4 contains EU-manufactured drug substance for 30-µg dosing; and Arm 5 contains US-manufactured drug substance for 20-µg dosing. In order to allow for balanced age representation across all arms, the randomization will be stratified by age groups: 12 through 17, 18 through 30, and 31 through 50 years.

Approximately 340 participants will be randomly assigned to each of the 3 US lots (Arms 1-3) and to the 20-µg arm (Arm 5) and approximately 170 participants will be randomly assigned to the EU lot (Arm 4), for a total of approximately 1530 randomized participants. It is expected that approximately 1224 evaluable participants will complete the study, based on a 20% nonevaluable rate. The duration of the study for each participant will be approximately 2 months. This study is observer-blinded, as the volumes of the 20-µg and the 30-µg doses of investigational vaccine are different.

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 2) separated by 21 days.

Blood samples will be collected at Visit 1 (Day 1/Vaccination 1) and Visit 3 (1 month after Dose 2) to assess immunogenicity; during the same visits, blood and nasal swab samples will be collected to detect past or current SARS-CoV-2 infection, respectively. Participants will be observed for 30 minutes after each vaccination and any reactions occurring during that time will be recorded as AEs. Local reactions, systemic events (including fever), and use of antipyretic medication occurring within 7 days after each vaccination will be collected via a provided e-diary (or e-diary application). AEs and SAEs will be collected from the signing of informed consent through and including Visit 3 (1 month after Dose 2). In addition, any AEs occurring up to 48 hours after the blood draw and nasal swab collection at Visit 3 must be recorded in the CRF.

Booster Study

Protocol amendment 2 added a booster study in which a subset of the adult participants (18 through 50 years of age) who each received two 30-µg doses of the designated US lot(s) will be randomly assigned to 1 of 2 arms in a 1:1 ratio as shown:

Arm Name	Study Intervention
Booster 1	BNT162b2 30 µg
Booster 2	BNT162b2.B.1.351 30 µg

Approximately 30 participants will be assigned to each arm for a total of 60 participants enrolled. It is expected that approximately 48 evaluable participants will complete the study, based on a 20% nonevaluable rate. The duration of the study for each participant will be approximately 1 month. This study is observer-blinded, to minimize changes in study conduct compared with the primary study.

Participants will receive a third dose of study intervention as randomized at Visit 4, 3 months after the receipt of Dose 2.

Blood samples will be collected at Visit 4 (Vaccination 3), Visit 5 (1 week after Dose 3),and Visit 6 (1 month after Dose 3) to assess immunogenicity; during the same visits, except Visit 5, blood and nasal swab samples will be collected to detect past or current SARS-CoV-2 infection, respectively. Participants will be observed for 30 minutes after the booster vaccination and any reactions occurring during that time will be recorded as AEs. Local reactions, systemic events (including fever), and use of antipyretic medication occurring within 7 days after the booster vaccination will be collected via a provided e-diary (or e-diary application). AEs and SAEs will be collected from Visit 4 through and including Visit 6 (1 month after Dose 3). In addition, any AEs occurring up to 48 hours after the blood draw and nasal swab collection at Visit 6 must be recorded in the CRF.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Study – Primary Immunogenicity Endpoints – Lot Comparisons

- Full-length S-binding IgG levels at 1 month after Dose 2 for participants receiving vaccine from the US lots (Arms 1, 2, and 3)

- Full-length S-binding IgG levels at 1 month after Dose 2 for participants receiving vaccine from the EU lot (Arm 4) and the 3 pooled US lots (pooled Arms 1, 2, and 3)

Concentrations of IgG levels will be determined in all participants at Visit 1 (Day 1) and Visit 3 (1 month after Dose 2) using the SARS-CoV-2 full-length S-binding IgG-level assay.

Values below the LLOQ will be set to 0.5 × LLOQ for the analysis. The LLOQ value for full-length S-binding IgG will be included in the analysis specification once it is available.

3.1.2. Primary Study – Primary Immunogenicity Endpoint – Dose Comparison

- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 for participants receiving 30-µg or 20-µg doses (prepared from the same manufacturing lot)

Titers will be determined in all participants at Visit 1 (Day 1) and Visit 3 (1 month after Dose 2) using the SARS-CoV-2 neutralizing assay.

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

3.1.3. Booster Study – Primary Immunogenicity Endpoints

- SARS-CoV-2 reference-strain neutralizing titers and SARS-CoV-2 B.1.351-strain neutralizing titers at each time point for participants receiving a third dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

- Fold rises in SARS-CoV-2 reference-strain neutralizing titers and SARS-CoV-2 B.1.351-strain neutralizing titers for participants receiving a third dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

- Seroresponse (≥4-fold increase from baseline) (based on neutralizing titers) to the SARS-CoV-2 reference strain and to the SARS-CoV-2 B.1.351 variant strain.

- Full-length S-binding IgG levels at each time point for participants receiving a third dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

- Fold rises in full-length S-binding IgG levels for participants receiving a third dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

Titers will be determined in all participants of the booster study at Visit 1 (Day 1), Visit 3 (1 month after Dose 2), Visit 4 (before Dose 3), Visit 5 (1 week after Dose 3), and Visit 6 (1 month after Dose 3) using the SARS-CoV-2 reference-strain and the SARS-CoV-2 B.1.351-strain neutralizing assays.

Concentrations of IgG levels will be determined in all participants of the booster study at Visit 1 (Day 1), Visit 3 (1 month after Dose 2), Visit 4 (before Dose 3), Visit 5 (1 week after Dose 3), and Visit 6 (1 month after Dose 3) using the SARS-CoV-2 full-length S-binding IgG-level assay.

Fold rises will be calculated for each participant of the booster study by taking the ratio of titers or IgG concentrations from a later time point to an earlier time point.

Seroresponse is defined as ≥4-fold increase from baseline (before Dose 1) to the specified time point. If the baseline measurement is below LLOQ, a postvaccination measurement of ≥4 × LLOQ is considered a seroresponse.

Values below the LLOQ for both full-length S-binding IgG and neutralizing titers will be set to 0.5 × LLOQ for the analysis. The LLOQ values for both will be included in the analysis specification once they are available.

3.1.4. Primary Safety Endpoints

The primary study and booster study have similar safety endpoints as follows:

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each dose

- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose
- AEs and SAEs from Dose 1 to 1 month after Dose 2 for participants in the primary study and from Dose 3 to 1 month after Dose 3 for participants in the booster study

3.1.4.1. Local Reactions

The local reactions assessed and reported in the e-diary are pain at the injection site, redness, and swelling, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

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

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

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

Note: Missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 4.

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

Table 4. Grading Scales for Local Reactions

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

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

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

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among the severity grades reported for that local reaction in the e-diary.

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive. Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasted 7 days or less, or the day the reaction ended if it continued beyond Day 7 (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). However, if a reaction is ongoing at the time of a subsequent dose, the end date/day for the ongoing event would be the date/day that the next dose is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset Day

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

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

3.1.4.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.4.1). Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 6 for summary of maximum temperature.

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

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

Table 5. Grading Scales for Systemic Events

Systemic Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea

Table 5. Grading Scales for Systemic Events

Systemic Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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.

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

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

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

Table 6. Ranges for Fever

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

3.1.4.3. Use of Antipyretic/Analgesic Medication

The use of antipyretic/analgesic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic/analgesic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.4.1), where applicable.

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

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

3.1.4.4. Adverse Events

AEs will be assessed from the time of informed consent through and including up to 48 hours after biospecimen collections at Visit 3 (1 month after Dose 2) for the participants in the primary study and from the time of receiving Dose 3 through and including up to 48 hours after biospecimen collections at Visit 6 (1 month after Dose 3) for the participants in the booster study. AEs will be categorized according to MedDRA terms.

The primary endpoints "AEs from Dose 1 to 1 month after Dose 2" in the primary study and "AEs from Dose 3 to 1 month after Dose 3" in the booster study and other supportive AE endpoints will be summarized by system organ class and preferred term at the participant level.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after each dose), and AESIs (confirmed COVID-19, MIS-C).

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

3.1.4.5. Serious Adverse Events

SAEs will also be collected from the time of informed consent through and including up to 48 hours after biospecimen collections at Visit 3 (1 month after Dose 2) for the participants in the primary study and from the time of receiving Dose 3 (Visit 4) through and including up to 48 hours after biospecimen collections at Visit 6 (1 month after Dose 3) for the participants in the booster study. SAEs will be categorized according to MedDRA terms.

The safety endpoints "SAEs from Dose 1 to 1 month after Dose 2" in the primary study and "SAEs from Dose 3 to 1 month after Dose 3" in the booster study will be summarized by system organ class and preferred term at the participant level. Additionally, the SAEs will be listed.

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

- Full-length S-binding IgG levels at baseline (before Dose 1) and 1 month after Dose 2 for participants receiving a 30-µg dose from different manufacturing lots (US and EU)

- Fold rises in full-length S-binding IgG levels from baseline (before Dose 1) to 1 month after Dose 2 for participants receiving a 30-µg dose from different manufacturing lots (US and EU)

- SARS-CoV-2 neutralizing titers at baseline (before Dose 1) and 1 month after Dose 2 for participants receiving 30-µg or 20-µg doses (prepared from the same manufacturing lot)

- Fold rises in SARS-CoV-2 neutralizing titers from baseline (before Dose 1) to 1 month after Dose 2 for participants receiving 30-µg or 20-µg doses (prepared from the same manufacturing lot)

Fold rises will be calculated for each participant by taking the ratio of titers or IgG concentrations from 1 month after Dose 2 to baseline.

3.3. Other Endpoints

Not applicable.

3.4. Baseline and Other Variables

Measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

Primary Study

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

Age at Dose 1 (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 19th birthday, the participant is considered to be 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of Dose 1 for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA.

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

Booster Study

The demographic variables for the booster study are defined as in the primary study except for age at Dose 3 (in years), which is derived using the date of birth and the Dose 3 date.

3.4.2. E-Diary Transmission

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

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment until the 1-month follow-up visit (Visit 3, primary study/Visit 6, booster study).
- Prohibited vaccines and medications listed in the protocol, Section 6.5.1, will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

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

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above (Section 3.1.4) in the Primary Safety Endpoints section.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Primary Study

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All participants who 1. are eligible and randomized; 2. receive 2 doses of vaccine to which they are randomized, with Dose 2 received within the predefined window (19-42 days, inclusive, after Dose 1); 3. have at least 1 valid immunogenicity result within an appropriate window 1 month after Dose 2 (28-42 days, inclusive, after Dose 2); 4. negative for both SARS-CoV-2 tests (RT-PCR and N-binding antibody assay) at both the Day 1 and 1-month post–Dose 2 visits; and 5. have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

Booster Study

Population	Description
Enrolled	All participants who sign the ICD at Visit 4.
Randomized	All participants who are assigned a randomization number at Visit 4 in the IRT system.
Booster evaluable immunogenicity	All participants who 1. are eligible and randomized; 2. receive 2 doses of vaccine to which they are randomized in the primary study with Dose 2 received within the predefined window (19-42 days, inclusive, after Dose 1) and receive Dose 3 to which they are randomized in the booster study with Dose 3 received with the predefined window (83 to 97 days, inclusive, after Dose 2); 3. have at least 1 valid immunogenicity result within an appropriate window 1 month after Dose 3 (28-42 days, inclusive, after Dose 3); 4. are negative for both SARS-CoV-2 tests (RT-PCR and N-binding antibody assay) at the Day 1 (Dose 1), 1-month post–Dose 2, Dose 3, and 1-month post–Dose 3 visits; and 5. have no other important protocol deviations as determined by the clinician.
Booster all-available immunogenicity	All randomized participants who receive Dose 3 of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 3.
Safety	All randomized participants who receive Dose 3 of the study intervention.

The important protocol deviations for both the primary study and booster study will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of Pfizer's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. Pfizer's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis.

In the primary study, for all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the all-available immunogenicity population if there is over 10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. The booster study will be assessed similarly.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

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

The majority of Pfizer staff will be blinded to study intervention allocation. The blinded study team will become unblinded to the primary study randomization information at the time of the database release of the primary study. These same study team members will remain blinded to the randomization information for the booster study until completion of that phase.

All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the testing for the primary study and for the booster study, respectively. Further details can be found in the protocol, Section 6.3. The timing for statistical analysis is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

Primary Study

There are 2 primary immunogenicity objectives on manufacturing lot comparisons. Hypothesis testing will be used to assess the first primary immunogenicity objective, the similarity of the immune response induced by BNT162b2 across the 3 US lots. The null hypothesis (H_{01}) is

$$H_{01}: |\ln(\mu_1)-\ln(\mu_2)| \geq \ln(1.5) \textit{ or } |\ln(\mu_1)-\ln(\mu_3)| \geq \ln(1.5) \textit{ or } |\ln(\mu_2)-\ln(\mu_3)| \geq \ln(1.5)$$

where ln(1.5) corresponds to a 1.5-fold equivalence margin, and ln(μ1), ln(μ2), and ln(μ3) are the natural log of the geometric mean of full-length S-binding IgG levels measured 1 month after Dose 2 from participants receiving BNT162b2 30 μg from the US lots in Arm 1, Arm 2, and Arm 3, respectively.

Two lots will be considered similar if the 2-sided 95% CI for the GMR is contained in the interval (0.67, 1.5). The 3 lots will be considered similar if the 1.5-fold equivalence criterion is met for all 3 between-lot comparisons (Arm 1 to Arm 2, Arm 1 to Arm 3, and Arm 2 to Arm 3).

Hypothesis testing will be used to assess the second primary immunogenicity objective, the similarity of the immune response induced by BNT162b2 30 μg in the EU lot to that in the US lots. The null hypothesis (H_{02}) is

$$H_{02}: |\ln(\mu_4)-\ln(\mu_p)| \geq \ln(1.5)$$

where ln(1.5) corresponds to a 1.5-fold equivalence margin, and $\ln(\mu_4)$ and $\ln(\mu_p)$ are the natural log of the geometric mean of full-length S-binding IgG levels measured 1 month after Dose 2 from participants receiving the BNT162b2 30 μg from the EU lot and the 3 pooled US lots, respectively.

The EU lot and the US lots will be considered similar if the 2-sided 95% CI for the GMR is contained in the interval (0.67, 1.5).

The primary immunogenicity objective on dose comparison is to assess the noninferiority of the immune response of the 20-μg dose to the standard 30-μg dose (prepared from the same lot). The null hypothesis is

$$H_{03}: \ln(\mu_{20})-\ln(\mu_{30}) \leq \ln(0.67)$$

where ln (0.67) corresponds to a 1.5-fold noninferiority margin and $\ln(\mu_{20})$ and $\ln(\mu_{30})$ are the natural log of the geometric mean of the SARS-CoV-2 neutralizing titers measured 1 month after Dose 2 from participants receiving the BNT162b2 20-μg dose or 30-μg dose (from the same US lot), respectively.

Noninferiority of the 20-µg dose to the corresponding 30-µg dose will be declared if the lower limit of the 2-sided 95% CI for the GMR is >0.67.

Booster Study

Not applicable.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

5.2. General Methods

Unless stated otherwise, "vaccine group" in this document refers to participants receiving any 1 of the three 30-µg US lots, the (30-µg) EU lot, or the 20-µg dose group in the primary study and to participants receiving BNT162b2 at 30 µg or BNT162b2.B.1.351 at 30 µg in the booster study. 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 Data

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

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[1]

5.2.2. Analyses for Continuous Data

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

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

5.2.2.1. Geometric Mean Ratios

Model-Based

As the primary approach in the primary study, 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.

Unadjusted

The GMRs in the primary study will be calculated as the mean of the difference of logarithmically transformed assay results between 2 vaccine groups and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.2. Geometric Means

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

5.2.2.3. Geometric Mean Fold Rises

GMFRs are defined as ratios of the results at a later time point to the results at an earlier time point. GMFRs are limited to participants with nonmissing values at both time points.

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

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.2.2.5. Antibody Response Curves

In the booster study, antibody response will be graphed for full-length S-binding IgG concentrations and SARS-CoV-2 neutralizing titers by vaccine group at baseline (before Dose 1) and at postvaccination blood sampling time points. The curves will display the geometric mean and 95% CI at each of the time points with a line connecting the geometric means for each vaccine group across time.

5.3. Methods to Manage Missing Data

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

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

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoints

6.1.1.1. Primary Study – Full-Length S-Binding IgG Concentrations at 1 Month After Dose 2 for Participants Receiving Vaccine From the US Lots

6.1.1.1.1. Main Analysis

- Estimands: GMR from one US lot to another lot (Arm 1/Arm 2, Arm 1/Arm 3, and Arm 2/Arm 3) (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: The GMRs and corresponding 95% CIs will be calculated using the linear regression model with terms of age and vaccine group as described in Section 5.2.2.1. The similarity will be assessed by comparing the limits of the 95% CI against the equivalence margins (Section 5.1.1).
- 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 GMC and the corresponding 95% CI for IgG concentrations will be presented for each US lot. The model-based estimate of GMR for each pair of lots being compared (Arm 1/Arm 2, Arm 1/Arm 3, and Arm 2/Arm 3) and the corresponding 95% CI will be calculated.

Figures:

A forest plot of GMRs with 95% CIs for each pair of lots being compared will be presented.

6.1.1.1.2. Sensitivity Analyses

- The main analysis will be repeated using an unadjusted GMR (Section 5.2.2.1).

6.1.1.2. Primary Study – Full-Length S-Binding IgG Concentrations at 1 Month After Dose 2 for Participants Receiving Vaccine From US and EU Lots

6.1.1.2.1. Main Analysis

- Estimands: GMR of the EU lot to the pooled US lots (Arm 4/pooled Arms 1, 2, and 3) (Section 2.1).

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

- Analysis time point: 1 Month after Dose 2.

- Analysis methodology: The GMR and corresponding 95% CI will be calculated using the linear regression model with terms of age and vaccine group as described in Section 5.2.2.1. The similarity will be assessed by comparing the limits of the 95% CI against the equivalence margins (Section 5.1.1).

- 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 GMC and the corresponding 95% CI for IgG concentration will be presented for the pooled US lots and the EU lot. The GMR of EU Lot 4 to the pooled US lots (Arm 4/pooled Arms 1, 2, and 3) and the corresponding 95% CI will be calculated.

Figures:

The GMR with 95% CI for comparison between the EU lot and the pooled US lots will be included in the forest plot described in Section 6.1.1.1.1.

6.1.1.2.2. Sensitivity Analyses

- The main analysis will be repeated using an unadjusted GMR (Section 5.2.2.1).

6.1.1.3. Primary Study – SARS-CoV-2 Neutralizing Titers at 1 Month After Dose 2 for Participants Receiving 20-µg Dose or 30-µg Dose

6.1.1.3.1. Main Analysis

- Estimands: GMR of the 20-µg dose to the 30-µg dose, both from the same manufacturing US lot (Arm 5/Arm 1) (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: The GMR and corresponding 95% CI will be calculated using the linear regression model with terms of age and vaccine group as described in Section 5.2.2.1. The noninferiority will be assessed by comparing the lower limits of the 95% CI against the noninferiority margins (Section 5.1.1).
- 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 GMT and the corresponding 95% CI for neutralizing titers will be presented for the 20-µg dose and the 30-µg dose. The model-based estimate of the GMR of the 20-µg dose to the 30-µg dose (Arm 5/Arm 1) and the corresponding 95% CI will be calculated.

6.1.1.3.2. Sensitivity Analyses

- The main analysis will be repeated using an unadjusted GMR (Section 5.2.2.1).

6.1.1.4. Booster Study – SARS-CoV-2 Reference-Strain Neutralizing Titers and SARS-CoV-2 B.1.351-Strain Neutralizing Titers at Each Time Point for Participants Receiving a Third Dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

6.1.1.4.1. Main Analysis

- Estimands: GMTs (Section 2.1).
- Analysis set: Booster evaluable immunogenicity population, booster all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3.
- Analysis methodology: Descriptive statistics.

- 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 GMTs and corresponding 2-sided 95% CIs at each specified time point will be presented for each vaccine group and each strain.

Figures:

- Empirical RCDCs will be presented separately for the SARS-CoV-2 reference-strain neutralizing titers and for the SARS-CoV-2 B.1.351-strain neutralizing titers for each vaccine group. There will be 2 figures, 1 for each strain. Each figure will display 10 curves, 1 for each of the time points, baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3, for each of the 2 vaccine groups. Only the booster evaluable immunogenicity population will be used.

- Antibody response line plot of GMTs and the associated 95% CIs will be presented at each of the time points, baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3, by vaccine group separately for each strain.

6.1.1.5. Booster Study – Fold Rises in SARS-CoV-2 Reference-Strain Neutralizing Titers and SARS-CoV-2 B.1.351-Strain Neutralizing Titers for Participants Receiving a Third Dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

6.1.1.5.1. Main Analysis

- Estimand: GMFRs (Section 2.1).

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

- Analysis time points: 1 Month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3.

- Analysis methodology: Descriptive statistics.

- 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 GMFRs from 1 month after Dose 2 to 1 week after and 1 month after Dose 3 as well as from before Dose 3 to 1 week after and 1 month after Dose 3 and corresponding 2-sided 95% CIs will be presented for each vaccine group and each strain.

6.1.1.6. Booster Study – Seroresponse (≥4-Fold Increase From Baseline) (Based on Neutralizing Titers) to the SARS-CoV-2 Reference Strain and to the SARS-CoV-2 B.1.351 Variant Strain

6.1.1.6.1. Main Analysis

- Estimands: Percentage of participants with seroresponse (Section 2.1).
- Analysis set: Booster evaluable immunogenicity population, booster all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3.
- Analysis methodology: Descriptive statistics.
- 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 percentages and corresponding 2-sided 95% CIs for the seroresponse (≥4-fold increase from baseline to the specific time point) to the reference strain and to the B.1.351 variant strain at 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3 will be presented separately, for each vaccine group.

6.1.1.7. Booster Study – Full-Length S-Binding IgG Levels at Each Time Point for Participants Receiving a Third Dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

6.1.1.7.1. Main Analysis

- Estimands: GMCs (Section 2.1).
- Analysis set: Booster evaluable immunogenicity population, booster all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3.
- Analysis methodology: Descriptive statistics.
- 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 GMCs and corresponding 2-sided 95% CIs for baseline, 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3 will be presented for each vaccine group.

Figures:

- Empirical RCDCs will be presented for the IgG concentrations for each vaccine group. The figure will display 10 curves, 1 for each of the time point, baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3, for each of the 2 vaccine groups. Only the booster evaluable immunogenicity population will be used.

- Antibody response line plot of GMCs and the associated 95% CIs will be presented at each of the time points, baseline (before Dose 1), 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3, by vaccine group.

6.1.1.8. Booster Study – Fold Rises in Full-Length S-Binding IgG Levels for Participants Receiving a Third Dose of BNT162b2 30 µg or BNT162b2.B.1.351 30 µg

6.1.1.8.1. Main Analysis

- Estimand: GMFRs (Section 2.1).

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

- Analysis time points: 1 Month after Dose 2, before Dose 3, and 1 Week after and 1 Month after Dose 3.

- Analysis methodology: Descriptive statistics.

- 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 GMFRs from 1 month after Dose 2 to 1 week after and 1 month after Dose 3 as well as from before Dose 3 to 1 week after and 1 month after Dose 3 and the corresponding 2-sided 95% CIs will be presented for each vaccine group.

6.1.2. Primary Safety Endpoints

Similar safety analyses will be performed separately for the participants in the primary study and the booster study.

6.1.2.1. Local Reactions

6.1.2.1.1. Main Analysis

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

- Analysis set: Safety population (Section 4).

- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- Reporting results: The proportion of participants reporting each local reaction after each dose will be summarized by maximum severity level and cumulatively across severity levels. The percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% 2-sided Clopper-Pearson CI will be presented for each vaccine group and the pooled US lots for the primary study and by vaccine group for the booster study.

6.1.2.1.2. Supplementary Analyses

As supplementary analyses to support the assessment of local reactions, the following endpoints (as defined in Section 3.1.4.1) will be summarized with the same analysis time point and analysis population:

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

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group and the pooled US lots for the primary study and by vaccine group for the booster study.

In addition, the proportions of participants reporting each prompted local reaction after any dose will be summarized by maximum severity level for the primary study.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days will be plotted for each dose by vaccine group and the pooled US lots for the primary study and by vaccine group for the booster study. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.2.2. Systemic Events

6.1.2.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose (Section 2.1).

- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- Reporting results: The proportion of participants reporting each systemic event after each dose will be summarized by maximum severity level and cumulatively across severity levels. The percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% 2-sided Clopper-Pearson CI will be presented for each vaccine group and the pooled US lots for the primary study and by vaccine group for the booster study.

6.1.2.2.2. Supplementary Analyses

As supplementary analyses to support the assessment of systemic events, the following endpoints (as defined in Section 3.1.4.2) will be summarized with the same analysis time point and analysis population:

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

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group and the pooled US lots for the primary study and by vaccine group for the booster study.

The use of antipyretic medication (see Section 3.1.4.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

In addition, the proportions of participants reporting each prompted systemic event after any dose will be summarized by maximum severity level for the primary study.

Figures:

Bar charts with the proportions of participants for each systemic event throughout 7 days will be plotted for each dose by vaccine group and the pooled US lots for the primary study and by vaccine group for the booster study. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.2.3. Adverse Events

6.1.2.3.1. Main Analysis

- Estimands: The percentages of participants reporting AEs from Dose 1 to 1 month after Dose 2 (Section 2.1) for the primary study and from Dose 3 to 1 month after Dose 3 for the booster study.

- Analysis set: Safety population (Section 4).

- Analysis time points: Dose 1 to 1 month after Dose 2 (primary study) and Dose 3 to 1 month after Dose 3 (booster study).

- Analysis methodology: Descriptive statistics described in Section 5.2.1.

- Intercurrent events and missing data: No missing values will be imputed except for partial AE start dates (Section 5.3).

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

6.1.2.3.2. Supplementary Analyses

As supplementary analyses to support the interpretation of the main analysis results, for participants in the primary study, descriptive summary statistics will also be provided by vaccine group and pooled US lots for related AEs and severe AEs, each from Dose 1 to 1 month after Dose 2. Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group and the pooled US lots if the number of immediate AEs is sufficiently large; otherwise, they will be listed only.

AEs that occurred after informed consent and before Dose 1 will not be included in the AE summary tables, but will be included in the AE listings.

Similar supplementary analyses will be repeated for participants in the booster study, for AEs collected from Dose 3 to 1 month after Dose 3, by vaccine group.

6.1.2.4. Serious Adverse Events

6.1.2.4.1. Main Analysis

- Estimands: The percentage of participants reporting SAEs from Dose 1 to 1 month after Dose 2 (Section 2.1) for the primary study and from Dose 3 to 1 month after Dose 3 for the booster study.

- Analysis set: Safety population (Section 4).

- Analysis time point: Dose 1 to 1 month after Dose 2 (primary study) and Dose 3 to 1 month after Dose 3 (booster study).

- Analysis methodology: Descriptive statistics.

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

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

6.2.1.1. Full-Length S-Binding IgG Levels

6.2.1.1.1. Main Analysis

- Estimands: GMCs (Section 2.1).

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

- Analysis time points: Baseline (before Dose 1) and 1 month after Dose 2.

- Analysis methodology: Descriptive statistics.

- 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 GMC and corresponding 2-sided 95% CIs for baseline and 1 month after Dose 2 will be presented for each vaccine group, as well as for the pooled US lots.

Figures:

Empirical RCDCs will be presented for the IgG concentrations for each vaccine group and the pooled US lots. There will be 2 figures, 1 for the 3 US lots and 1 for the pooled US lots, and the EU lot. Each figure will display 6 or 4 curves respectively, one for baseline (Day 1) and one for 1 month after Dose 2, for each of the vaccine groups or the pooled US lots. Only the evaluable immunogenicity population will be used.

6.2.1.2. Fold Rises in Full-Length S-Binding IgG Levels From Baseline to 1 Month After Dose 2

6.2.1.2.1. Main Analysis

- Estimand: GMFRs (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1) and 1 month after Dose 2.
- Analysis methodology: Descriptive statistics.
- 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 GMFRs at 1 month after Dose 2 and corresponding 2-sided 95% CIs will be presented for each vaccine group and the pooled US lots.

6.2.1.3. SARS-CoV-2 Neutralizing Titers

6.2.1.3.1. Main Analysis

- Estimands: GMTs for the 20-µg dose (Arm 5) and the 30-µg dose (Arm 1) (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1) and 1 month after Dose 2.
- Analysis methodology: Descriptive statistics.
- 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 GMT and corresponding 2-sided 95% CIs for baseline and 1 month after Dose 2 will be presented for each dose group.

Figures:

Empirical RCDCs will be presented for the neutralizing titers for each dose. The figure will display 4 curves, one for baseline (Day 1) and one for 1 month after Dose 2, for each of the dose groups. Only the evaluable immunogenicity population will be used.

6.2.1.4. Fold Rises in SARS-CoV-2 Neutralizing Titers From Baseline to 1 Month After Dose 2

6.2.1.4.1. Main Analysis

- Estimand: GMFRs for the 20-µg dose (Arm 5) and the 30-µg dose (Arm 1) (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1) and 1 month after Dose 2.
- Analysis methodology: Descriptive statistics.
- 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 GMFRs at 1 month after Dose 2 and corresponding 2-sided 95% CIs will be presented for each dose group.

6.3. Other Endpoints

Not applicable.

6.4. Subset Analyses

Subgroup analyses by age group (12 through 17, 18 through 30, and 31 through 50 years), sex (male and female) and race (white, Asian, African American, and others [the rest combined]) will be performed for the following immunogenicity and safety endpoints in the primary study. No subset analyses are planned for the booster study.

6.4.1. Immunogenicity

- GMCs and associated 2-sided 95% CIs for full-length S-binding IgG levels at baseline and 1 month after Dose 2 will be summarized by vaccine group (Arm 1 through Arm 4) and pooled US lots for each subgroup.
- GMTs and associated 2-sided 95% CIs for SARS-CoV-2 neutralizing titers at baseline and 1 month after Dose 2 will be summarized by dose group (20 µg [Arm 5] and 30 µg [Arm 1]) for each subgroup.

6.4.2. Safety

Descriptive summary statistics for the following endpoints will be provided by vaccine group and pooled US lots for each subgroup:

- Proportion of participants reporting local reactions, by maximum severity level.

- Proportion of participants reporting systemic events, by maximum severity level.
- Proportion of participants reporting AEs within 1 month after Dose 2, by system organ class and preferred term.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Primary Study

Demographic characteristics, including age at Dose 1, sex, race, and ethnicity, will be summarized using descriptive statistics for each vaccine group, the pooled US lots, and overall. The summary will be provided for the safety population and the evaluable immunogenicity population.

Booster Study

Similar summaries will be repeated by vaccine group for the booster study, except for age, which will be calculated at Dose 3.

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 in the primary study with at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group, pooled US lots, and overall for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

Primary Study

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (Doses 1 and 2), who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment), pooled US lots, and overall. The reasons for withdrawal will be those as specified in the database.

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

Booster Study

Similar summaries will be repeated by vaccine group for the booster study.

6.5.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for baseline (before Dose 1) and 1 month after Dose 2 for the primary study and baseline, 1 month after Dose 2, before Dose 3, and 1 week after and 1 month after Dose 3 for the booster study.

6.5.2.3. E-Diaries

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

The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

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

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

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

Similarly, summaries and listings will be generated for the booster study by vaccine group.

6.5.4. Prior/Concomitant Vaccinations and Concomitant Medications

In the primary study, each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before Dose 1 will be listed. The number and percentage of participants receiving each concomitant vaccine after Dose 1 of study intervention will be tabulated for each vaccine group and the pooled US lots for all participants in the safety population. Similar summarization will be done separately for concomitant medications received. Transfusions and radiation treatments received, if any, will be listed.

Similarly, summaries and listings for concomitant vaccines and prohibited medications will be generated for the booster study.

6.6. Safety Summaries and Analyses

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs, are described in the Primary Safety Endpoints section (see Section 6.1.2).

7. INTERIM ANALYSES

7.1. Introduction

No interim analysis is planned in this study. A program-wide EDMC will monitor the safety data for this study.

7.2. Analysis Timings

Statistical analyses are planned to be carried out after the complete study data are available and the database is locked. CCI [redacted]

8. REFERENCES

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

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BDR	blinded data review
BLQ	below limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
EMA	European Medicines Agency
EU	European Union
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
ICD	informed consent document
IgG	immunoglobulin G
IRT	interactive response technology
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
N/A	not applicable
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
US	United States
WHO	World Health Organization