



Protocol C4591020

**A PHASE 3, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE
SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MULTIPLE
FORMULATIONS OF THE VACCINE CANDIDATE BNT162b2 AGAINST
COVID-19 IN HEALTHY ADULTS 18 THROUGH 55 YEARS OF AGE**

**Statistical Analysis Plan
(SAP)**

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 6 Apr 2021	Original 18 Jan 2021	N/A	N/A
2 05 May 2021	Amendment 1 15 Apr 2021	Align with protocol amendment 1	<ul style="list-style-type: none">• Changed study title.• Removed second primary objective from Table 2, Section 3.1, Section 5.1.1, and Section 6.1.1.• Added exploratory objectives/endpoints to Table 2, Section 3.3, and Section 6.3.1.• Updated the study design and planned number of participants required for Part 2 of the study in Section 2.2.• Updated Section 5.1.2 to reflect that there is now only 1 primary objective.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591020. 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 to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population ([Section 4](#)) and are described in [Table 2](#). 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 $0.5 \times \text{LLOQ}$ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

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

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
<ul style="list-style-type: none"> To demonstrate that the immune response induced by lyophilized BNT162b2 in SDVs is noninferior to the immune response induced by frozen-liquid BNT162b2 in MDVs in participants without evidence of SARS-CoV-2 infection during the study. 	In participants complying with the key protocol criteria (evaluable participants): <ul style="list-style-type: none"> GMR of lyophilized formulation in SDVs to frozen-liquid formulation in MDVs 1 month after Dose 2. 	<ul style="list-style-type: none"> Full-length S-binding IgG levels.
Primary Safety Objectives	Estimands	Primary Safety Endpoints
<ul style="list-style-type: none"> To evaluate the safety of BNT162b2 when administered on a 2-dose schedule in healthy adults 18 through 55 years of age. 	In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants reporting: <ul style="list-style-type: none"> 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 through 1 month after Dose 2. 	<ul style="list-style-type: none"> 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.
Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
<ul style="list-style-type: none"> To describe the immune responses induced by lyophilized BNT162b2 in SDVs and frozen-liquid BNT162b2 in MDVs. 	In evaluable participants from each vaccine group: <ul style="list-style-type: none"> GMCs at baseline (before Dose 1) and 1 month after Dose 2. GMFR from baseline (before Dose 1) to 1 month after Dose 2. 	<ul style="list-style-type: none"> Full-length S-binding IgG levels.
Exploratory Objectives	Estimands	Exploratory Endpoints
<ul style="list-style-type: none"> To describe the immune responses induced by frozen-liquid BNT162b2 with LNP size at the upper end of specification and RTU BNT162b2 in participants without evidence of SARS-CoV-2 infection during the study. 	In evaluable participants: <ul style="list-style-type: none"> GMR of frozen-liquid BNT162b2 with LNP size at the upper end of specification relative to frozen-liquid BNT162b2 in MDVs 1 month after Dose 2. GMR of RTU formulation relative to lyophilized formulation in SDVs 1 month after Dose 2. 	<ul style="list-style-type: none"> Full-length S-binding IgG levels and/or SARS-CoV-2 neutralizing titers.
<ul style="list-style-type: none"> To describe the immune responses induced by frozen-liquid BNT162b2 with LNP size at the upper end of specification and RTU BNT162b2. 	In evaluable participants from each vaccine group: <ul style="list-style-type: none"> GMCs and/or GMTs at baseline (before Dose 1) and 1 month after Dose 2. GMFR from baseline (before Dose 1) to 1 month after Dose 2. 	<ul style="list-style-type: none"> Full-length S-binding IgG levels and/or SARS-CoV-2 neutralizing titers.

2.2. Study Design

This is a Phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of BNT162b2, an RNA-based COVID-19 vaccine, administered on a 2-dose schedule in healthy adults 18 through 55 years of age. The study will be conducted in the United States with potential to expand to other countries.

In Part 1, participants will be randomized in a 1:1 ratio to 1 of the 2 groups (lyophilized SDV or frozen-liquid MDV control for lyophilized SDV). Separately, in Part 2, participants will be randomized in a 1:1 ratio to 1 of the 2 groups (frozen-liquid BNT162b2 with LNP size at the upper end of specification or RTU BNT162b2). The duration of the study for each participant will be approximately 2 months.

Approximately 550 participants will be randomly assigned to 1 of the 2 vaccine groups in Part 1 (lyophilized SDV, frozen-liquid MDV control for lyophilized SDV); separately, approximately 60 participants will be randomly assigned to 1 of the 2 vaccine groups in Part 2 (frozen-liquid BNT162b2 with LNP size at the upper end of specification or RTU BNT162b2) for a total of approximately 610 randomized participants. It is expected that approximately 488 evaluable participants will complete the study, based on a 20% nonevaluable rate.

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 2) separated by 21 days in accordance with the study's SoA.

Blood samples will be collected at Visit 1 (Day 1/Vaccination 1) and Visit 3 (1 month after Dose 2) to assess immunogenicity and to detect past SARS-CoV-2 infection. During the same visits nasal swab samples will be collected to detect current SARS-CoV-2 infection. 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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

- Full-length S-binding IgG levels at 1 month after Dose 2 for participants receiving lyophilized formulation in SDVs or frozen-liquid formulation in MDVs.

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 $0.5 \times \text{LLOQ}$ 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 Safety Endpoints

- 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 through 1 month after Dose 2.

3.1.2.1. 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 as 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 absent, 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 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.

3.1.2.2. 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 3.1.2.1](#)). 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 absent, 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
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 $\geq 38.0^{\circ}\text{C}$ (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 $<35.0^{\circ}\text{C}$ and $>42.0^{\circ}\text{C}$ will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to [Table 6](#).

If a fever of $\geq 39.0^{\circ}\text{C}$ (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 $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$). If a participant experiences a confirmed fever $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$), 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)

3.1.2.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic 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 3.1.2.1](#)), where applicable.

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

3.1.2.4. 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). AEs will be categorized according to MedDRA terms.

The primary endpoint “AEs from Dose 1 through 1 month after Dose 2” and other supportive AE endpoints will be summarized by system organ class and preferred term at the participant level.

This primary endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose).

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](#).

3.1.2.5. 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). SAEs will be categorized according to MedDRA terms.

The safety endpoint “SAEs from Dose 1 through 1 month after Dose 2” 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 in Part 1 only.
- Fold rises in full-length S-binding IgG levels from baseline (before Dose 1) to 1 month after Dose 2 in Part 1 only.

3.3. Exploratory Endpoints

- Full-length S-binding IgG levels and/or SARS-CoV-2 neutralizing titers at 1 month after Dose 2 for participants receiving frozen-liquid BNT162b2 with LNP size at the upper end of specification, frozen-liquid BNT162b2 in MDVs, RTU BNT162b2, and lyophilized formulation of BNT162b2 in SDVs.

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

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), 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.

3.4.2. E-Diary Transmission

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

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment until the 1-month post–Dose 2 visit (Visit 3).
- 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 3.1.2](#)) in the primary safety endpoints.

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 vaccine or vaccine actually 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.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All participants who <ol style="list-style-type: none"> 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 to 42 days, inclusive, after Dose 1), 3. have at least 1 valid and determinate immunogenicity result within an appropriate window at 1 month after Dose 2 (28 to 42 days, inclusive, after Dose 2), 4. are 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 participants who receive at least 1 dose of the study intervention and have at least 1 valid and determinate immunogenicity result after vaccination.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

The important protocol deviations 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.

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 safety analyses will be based on the 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. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. 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

The primary immunogenicity objective is to assess the noninferiority of the immune response induced by lyophilized SDV BNT162b2 compared to frozen-liquid MDV BNT162b2. The null hypothesis (H_0) is

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

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

- $\ln(\mu_1)$ is the natural log of the geometric mean of full-length S-binding IgG levels measured 1 month after Dose 2 from participants receiving lyophilized SDV BNT162b2;
- $\ln(\mu_2)$ is the natural log of the geometric mean of full-length S-binding IgG levels measured 1 month after Dose 2 from participants receiving frozen-liquid MDV BNT162b2 control for lyophilized SDV

Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR of lyophilized SDV relative to the corresponding frozen-liquid MDV control is greater than 0.67 (1.5-fold criterion).

5.1.2. Multiplicity Considerations

There is only 1 hypothesis for the primary immunogenicity endpoint, and within-group descriptive summaries will be provided for the secondary immunogenicity endpoint. Consequently, no multiplicity adjustments are applied.

5.2. General Methods

Unless stated otherwise, “vaccine group” in this section refers to participants receiving lyophilized SDV, frozen-liquid MDV control for lyophilized SDV, frozen-liquid BNT162b2 with LNP size at the upper end of specification, or RTU BNT162b2. 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 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

The GMRs 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 after vaccination to the results before vaccination. GMFRs are limited to participants with nonmissing values at both time points.

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

5.2.2.4. 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.

5.3. 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 of 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 and 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 $0.5 \times \text{LLOQ}$ 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 Endpoint

6.1.1.1. Full-Length S-Binding IgG Concentrations at 1 Month After Dose 2 for Participants Receiving Lyophilized Formulation in SDVs or Frozen-Liquid Formulation in MDVs

6.1.1.1.1. Main Analysis

- Estimand: GMR of lyophilized formulation in SDVs to frozen-liquid formulation in MDVs ([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 method described in [Section 5.2.2.1](#). The noninferiority will be assessed by comparing the lower limit of the 95% CI against the noninferiority criterion ([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 observed GMCs and 95% CIs for IgG concentration will be presented for lyophilized SDV and frozen-liquid MDV. The GMR for the comparison and the corresponding 95% CI will be calculated.

6.1.2. Primary Safety Endpoints

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: 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.

6.1.2.1.2. Supplementary Analyses

As supplementary analyses to support the assessment of local reactions, the following endpoints (as defined in [Section 3.1.2.1](#)) 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.

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

Figures:

Bar charts with the proportions of participants for each local reaction on each day (Day 1 through Day 7) and any day (Day 1 through Day 7) will be plotted for each vaccine group after each dose, with different patterns displayed in the bar charts for different severity levels (each day) and different maximum severity levels for any day, respectively.

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: 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.

6.1.2.2.2. Supplementary Analyses

As supplementary analyses to support the assessment of systemic events, the following endpoints (as defined in [Section 3.1.2.2](#)) 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.

The use of antipyretic medication (see [Section 3.1.2.3](#)) 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.

Figures:

Bar charts with the proportions of participants for each systemic event on each day (Day 1 through Day 7) and any day (Day 1 through Day 7) will be plotted for each vaccine group after each dose, with different patterns displayed in the bar charts for different severity levels (each day) and different maximum severity levels for any day, respectively.

6.1.2.3. Adverse Events

6.1.2.3.1. Main Analysis

- Estimand: The percentages of participants reporting AEs from Dose 1 through 1 month after Dose 2 ([Section 2.1](#)).
- Analysis set: Safety population ([Section 4](#)).
- Analysis time point: Dose 1 through 1 month after Dose 2.

- 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.

6.1.2.3.2. Supplementary Analyses

As supplementary analyses to support the interpretation of the main analysis results, descriptive summary statistics will also be provided by vaccine group for related AEs and severe AEs, each from Dose 1 through 1 month after Dose 2. Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group, 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.

6.1.2.4. Serious Adverse Events

6.1.2.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 1 through 1 month after Dose 2 ([Section 2.1](#)).
- Analysis set: Safety population ([Section 4](#)).
- Analysis time point: Dose 1 through 1 month after Dose 2.
- 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.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

6.2.1.1. Full-Length S-Binding IgG Levels in Participants Receiving Lyophilized BNT162b2 in SDVs or Frozen-Liquid BNT162b2 in MDVs

6.2.1.1.1. Main Analyses

- Estimand: 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 GMCs and corresponding 2-sided 95% CIs for baseline and 1 month after Dose 2 will be presented for each vaccine group.

Figures:

Empirical RCDCs will be presented for the IgG concentrations for each vaccine group. The 2 vaccine groups will be displayed in 1 figure. The figure will display 4 curves, one for baseline (Day 1) and one for 1 month after Dose 2, for each of the vaccine groups. Only the evaluable immunogenicity population will be used.

6.2.1.2. Fold Rises in Full-Length S-Binding IgG Levels From Baseline Through 1 Month After Dose 2 in Participants Receiving Lyophilized BNT162b2 in SDVs or Frozen-Liquid BNT162b2 in MDVs

- Estimand: GMFRs ([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: 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.

6.3. Other Endpoints

6.3.1. Exploratory Endpoints

6.3.1.1. Full-Length S-Binding IgG Concentrations and/or SARS-CoV2 Neutralizing Titers at 1 Month after Dose 2 for Participants Receiving Frozen-Liquid BNT162b2 with LNP Size at Upper End of Specification or Frozen-Liquid BNT162b2 in MDVs

- Estimand: GMR of frozen-liquid BNT162b2 with LNP size at upper end of specification relative to frozen-liquid BNT162b2 in MDVs ([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 method described in [Section 5.2.2.1](#). A random sample of 30 participants receiving frozen-liquid BNT162b2 in MDVs will be selected from Part 1 of the study for this analysis.
- 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 observed GMCs for IgG concentration and/or GMTs for SARS-CoV-2 neutralizing titers and 95% CIs will be presented for frozen-liquid BNT162b2 with LNP size at upper end of specification and frozen-liquid BNT162b2 in MDVs. The GMR for the comparison and the corresponding 95% CI will be calculated.

6.3.1.2. Full-Length S-Binding IgG Concentrations and/or SARS-CoV2 Neutralizing Titers at 1 Month after Dose 2 for Participants Receiving RTU BNT162b2 or Lyophilized BNT162b2 in SDVs

- Estimand: GMR of RTU BNT162b2 relative to lyophilized BNT162b2 in SDVs ([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 method described in [Section 5.2.2.1](#). A random sample of 30 participants receiving lyophilized BNT162b2 in SDVs will be selected from Part 1 of the study for this analysis.

- 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 observed GMCs for IgG concentrations and/or GMTs for SARS-CoV-2 neutralizing titers and 95% CIs will be presented for RTU BNT162b2 and lyophilized BNT162b2 in SDVs. The GMR for the comparison and the corresponding 95% CI will be calculated.

6.3.1.3. Full-Length S-Binding IgG Concentrations and/or SARS-CoV2 Neutralizing Titers at 1 Month after Dose 2 for Participants Receiving Frozen-Liquid BNT162b2 with LNP Size at Upper End of Specification or RTU BNT162b2

- Estimand: GMCs and/or GMTs ([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 GMCs and/or GMTs and the corresponding 2-sided 95% CIs for baseline and 1 month after Dose 2 will be presented for each vaccine group.

Figures:

Empirical RCDCs will be presented for the IgG concentrations and/or SARS-CoV-2 neutralizing titers for each vaccine group. The 2 vaccine groups will be displayed in 1 figure. The figure will display 4 curves, one for baseline (Day 1) and one for 1 month after Dose 2, for each of the vaccine groups. Only the evaluable immunogenicity population will be used.

6.3.1.4. Fold Rises in Full-Length S-Binding IgG Levels From Baseline Through 1 Month After Dose 2 for Participants Receiving Frozen-Liquid BNT162b2 with LNP Size at Upper End of Specification or RTU BNT162b2

- Estimand: GMFRs ([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: 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.

6.4. Subset Analyses

Subgroup analyses by sex (male and female) and race (white, African American, and others [the rest combined]) will be performed for the following immunogenicity and safety endpoints for Part 1 of the study.

6.4.1. Immunogenicity

GMCs of full-length S-binding IgG concentrations and associated 2-sided 95% CIs at baseline and 1 month after Dose 2 will be summarized by vaccine group for each subgroup.

6.4.2. Safety

Descriptive summary statistics for the following endpoints will be provided by vaccine group 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

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

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 system organ class and preferred term level, will be summarized by vaccine group and overall for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (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) 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.

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.

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.

The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

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 and overall for all randomized participants. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall.

A listing of participants who received a vaccine other than that 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.

6.5.4. 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 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 for all participants in the safety population. Similar summarization will be done separately for concomitant medications received.

6.6. Safety Summaries and Analyses

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs, are described under the Primary Safety Endpoints (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 will be carried out when the final data for specified objectives for a given study part are available while the study is ongoing.

8. REFERENCES

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

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BLQ	below the limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IgG	immunoglobulin G
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MDV	multidose vial
MedDRA	Medical Dictionary for Regulatory Activities
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RTU	ready-to-use
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
SDV	single-dose vial
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SoA	schedule of activities
WHO	World Health Organization