Protocol C4591005

A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, AND OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE AGAINST COVID-19 IN HEALTHY JAPANESE ADULTS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 18Nov2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
1 / 16Nov2020	Protocol Amendment 2 (22Oct2020)	N/A
2 / 18Nov2021	Protocol Amendment 3 (17Mar2021)	Section 2.2.1 Added revision of study design to match the PRT amendment 3 Section 3.1.1.4 Minor revision of description of AEs to match the PRT description Section 3.2 Updated the definition of subgroup analysis Section 3.3.1 Updated the definition of subgroup analysis Section 4 Minor revision of description Section 6.1.1.3.2 Added generation of AESI listing Section 6.1.2.1.2 and Section 6.2.1.1.2 Added the definition of positive SARS-CoV-2 at baseline Section 6.3.1.1.1 Updated the description in line with that in Section 3.3.1 Section 6.3.1.2 Updated the analysis set for the summary Section 6.4.2.1 Added summary of disposition to reflect revision of study design in PRT amendment 3 Section 6.4.3.1 Added summary of vaccination timing and administration to reflect revision of study design in PRT amendment 3 Section 6.4.5 Added summary of AEs to reflect revision of study design in PRT amendment 3

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591005. 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.

[redacted]

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 2 below.

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

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (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 antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

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

Objectives	Estimands	Endpoints
Primary Safety:		
To describe the safety and tolerability profiles of a prophylactic BNT162 vaccine in healthy Japanese adults after 2 doses	In participants receiving at least 1 dose of study intervention, 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 from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 12 months 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
	In addition, in a clinical laboratory subset, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Hematology and chemistry laboratory parameters detailed in the protocol, Section 10.2.

[redacted]

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

Objectives	Estimands	Endpoints
Primary Immunogenicity:		
To describe the immune responses elicited by a prophylactic BNT162 vaccine in healthy Japanese adults	In participants complying with the key protocol criteria (evaluable participants): • GMTs 1 month after Dose 2 • GMFR from before vaccination to 1 month after Dose 2	• SARS-CoV-2 serum neutralizing titers
Secondary Immunogenicity:		
To describe the immune responses elicited by a prophylactic BNT162 vaccine in healthy Japanese adults	In the evaluable participants, at baseline, 21 days after Dose 1; 7 and 14 days and 6 and 12 months after Dose 2: • GMTs at each time point • GMFR from before vaccination to each subsequent time point after vaccination	• SARS-CoV-2 serum neutralizing titers
To describe the immune responses elicited by prophylactic BNT162 vaccine in participants with/without confirmed COVID-19 before Dose 2	In evaluable participants, at baseline, 21 days after Dose 1; 7 and 14 days and 1, 6 and 12 months after Dose 2: • GMTs at each time point • GMFR from before vaccination to each subsequent time point after vaccination	• SARS-CoV-2 serum neutralizing titers
Exploratory Immunogenicity:		
To describe the immune responses elicited by prophylactic BNT162 vaccine in participants with/without confirmed COVID-19 during the study	In the evaluable participants, at baseline, 21 days after Dose 1; 7 and 14 days and 1, 6, and 12 months after Dose 2: • GMTs at each time point • GMFR from before vaccination to each subsequent time point after vaccination	• SARS-CoV-2 serum neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with/without confirmed COVID-19 during the study		• SARS-CoV-2 N-binding antibody

[redacted]

2.2. Study Design

2.2.1. Overall Design

This is a Phase 1/2, randomized, placebo-controlled, and observer-blind study in healthy Japanese adults.

The study will evaluate the safety, tolerability, and immunogenicity of the SARS-CoV-2 RNA vaccine candidate against COVID-19 (BNT162b2), which is the same as the vaccine candidate selected for Phase 2/3 evaluation in C4591001 study:

- As 2 doses, separated by 21 days.
- At 30-µg dose level.
- In adults 20 to 85 years of age.

Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain), and use of antipyretic medication usage will be prompted for and collected by all participants in an e-diary from Day 1 through Day 7 after each administration of study intervention. AEs will be collected from the time the participant provides informed consent through 1 month after Dose 2, and SAEs will be collected from the time of informed consent through 12 months after Dose 2.

As this study is the first study conducted in Japan, clinical laboratory tests will be performed in the first 24 participants (12 participants 20 to 64 years of age and 12 participants 65 to 85 years of age) (clinical laboratory subset). After randomization of all participants in the clinical laboratory subset is completed, the other participants will be enrolled.

Blood will be collected prior to Dose 1, prior to Dose 2, 7 and 14 days, and 1, 6, and 12 months after Dose 2 to assess immunogenicity.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants.

Participants are expected to participate for up to a maximum of approximately 14 months.

From protocol amendment 3, this study was transitioned from a clinical trial to a postmarketing study according to the Japanese regulation because BNT162b2 was approved by the MHLW on 14-February-2021.

[redacted]

All participants were informed of their original study intervention allocation (BNT162b2 or placebo) by the site staff. All participants who originally received placebo were offered the opportunity to receive BNT162b2 at their earliest convenience as part of the study (administration of BNT162b2 before the 6-month follow-up visit [Visit 8 for the clinical laboratory subset or Visit 6 for the standard participants] was allowed). If they wanted to receive BNT162b2, they were moved to the SoA (Section 1.3.3) in the protocol for their remaining visits. Participants who originally received BNT162b2 and placebo recipients who declined BNT162b2 vaccination were continued in the study as originally planned.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each dose in each vaccine group.
- Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose in each vaccine group.
- AEs from Dose 1 to 1 month after Dose 2.
- SAEs from Dose 1 to 12 months after Dose 2.

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7 after 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 the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 for each dose, where Day 1 is the day of each dose, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7);
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

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

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

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of each local reaction.	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).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.
Presence of any local reaction.	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).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for each and any of the local reactions (redness, swelling, and pain at the injection site) and for each and any of the severe local reactions within the interval from Day 1 through Day 7 after each dose.

Severity and Maximum Severity

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

Table 4. Local Reaction Grading Scale

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

[redacted]

For each local reaction reported for 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 where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 4), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. However, if a reaction is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing event would be the date/day that the next vaccine 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 any severity.

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

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the way local reactions are handled for presence of event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.1.1). 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 symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

[redacted]

Table 5. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

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 axillary temperature of ≥37.5°C. The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place. Fever will be grouped into ranges for the analysis according to Table 6 below.

Table 6. Scale for Fever

≥37.5°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

Note: Fever is defined as axillary temperature ≥37.5°C.

[redacted]

3.1.1.3. 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 3.1.1.1), where applicable.

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

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

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after Dose 2.

The primary endpoint "AEs from Dose 1 to 1 month after Dose 2" and other AE endpoints will be summarized by SOC and PT 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. Standard algorithms for handling missing AE dates will be applied as described in the Pfizer Vaccine data standard rules.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan.
- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 4 of participants with the AE term in at least 1 vaccine group.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

Confirmed COVID-19 diagnosis (SARS-CoV-2 positive test) will be collected as an AESI from the time the participant provides informed consent until study completion (Month 12 (Visit 9) for the clinical laboratory subset, Month 12 (Visit 7) for standard participants).

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent to approximately 12 months after Dose 2 of study intervention.

The safety endpoint "SAEs from Dose 1 to 12 months after Dose 2" will be summarized by SOC and PT at the participant level.

3.1.1.6. Hematology and Chemistry Laboratory Parameters

For the clinical laboratory subset, below are the additional primary safety endpoints:

- Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2.

- Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2.

The following safety laboratory tests will be performed at the times defined in the protocol, Section 1.3 (schedule of activities). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 7). Additionally, the primary criterion for abnormality will follow the Pfizer safety rule book.

[redacted]

Table 7. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm^3	2500 – 3500	1500 – 2499	1000 – 1499	<1000
Lymphocytes decrease - cells/mm^3	750 – 1000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1500 – 2000	1000 – 1499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Alkaline phosphate - increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	>10 × ULN
Liver function tests - ALT, AST increase by factor	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10 × ULN
Bilirubin - when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	>1.75 × ULN
Bilirubin - when liver function test is normal - increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	>3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

3.1.2. Primary Immunogenicity Endpoints

In participants complying with the key protocol criteria (evaluable participants), at the following time point after receipt of study intervention:

- 1 month after Dose 2.

Below are the primary immunogenicity endpoints:

- SARS-CoV-2 serum neutralizing titers.

[redacted]

Titers above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

3.2. Secondary Immunogenicity Endpoints

In evaluable participants, at the following time points:

- Baseline, 21 days after Dose 1; 7 and 14 days and 6 and 12 months after Dose 2.

Below are the secondary immunogenicity endpoints:

- SARS-CoV-2 serum neutralizing titers.

Also, secondary immunogenicity endpoints will be described in healthy Japanese evaluable participants with/without confirmed COVID-19 before Dose 2 at the following time points:

- Baseline (only for GMTs), 21 days after Dose 1; 7 and 14 days and 1, 6, and 12 months after Dose 2.

Participants "with confirmed COVID-19 before Dose 2" for the subgroup analysis in the protocol are defined as those who reported confirmed COVID-19 diagnosis as an AESI by Visit 4 (clinical laboratory subset) or Visit 2 (standard participants) in Section 3.1.1.4.

3.3. Other Endpoints

3.3.1. Exploratory Immunogenicity Endpoints

Exploratory immunogenicity endpoints will be described in healthy evaluable Japanese participants with/without confirmed COVID-19 during the study at the following time points after receipt of study intervention:

- Baseline (only for GMTs), 21 days after Dose 1; 7 and 14 days and 1, 6 and 12 months after Dose 2.

Participants "with confirmed COVID-19 during the study" for the subgroup analysis in the protocol are defined as those who reported confirmed COVID-19 diagnosis as an AESI by Visit 9 (clinical laboratory subset) or Visit 7 (standard participants) in Section 3.1.1.4.

Below are the immunogenicity endpoints:

- SARS-CoV-2 serum neutralizing titers.

- SARS-CoV-2 N-binding antibody assay.

A positive SARS-CoV-2 N-binding antibody result after vaccination in a participant with a negative SARS-CoV-2 N-binding antibody result at baseline will be considered seroconversion to SARS-CoV-2.

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 (Asian), racial designation (Japanese) and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported).

Age at the time of vaccination (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 21st birthday, the participant is considered to be 20 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at 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 baseline clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, 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 Completion

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 items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

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 6-month follow-up visit (Visit 8 for clinical laboratory subset, Visit 6 for the other participants).

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the primary safety endpoints.

[redacted]

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per SOPs.

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 eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood collection within an appropriate window after Dose 2 (within 28-42 days after Dose 2), and 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 investigational product with at least 1 valid immunogenicity result after vaccination. Participants will be grouped as randomized in the immunogenicity analysis.
Safety	All randomized participants who receive at least 1 dose of the study intervention. Participants will be grouped according to the vaccine as administered in the safety analysis.

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

Both evaluable and all-available populations will be used for immunogenicity analyses. If there is less than a 10% difference in the total number of participants included between the all-available and evaluable populations, only the evaluable population will be used in the analysis of immunogenicity results.

5. GENERAL METHODOLOGY AND CONVENTIONS

To facilitate rapid review of data in real time, Sponsor staff will be unblinded 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 protocol, Section 6.3. The timing for statistical analyses is specified in Section 7.

5.1. Hypotheses and Decision Rules

No hypothesis will be performed testing for this study.

[redacted]

5.2. General Methods

Time points for local reactions and systemic events refer to data within 7 days after each dose. 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% CIs where applicable.

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

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen[2] method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

5.2.2. Analyses for Continuous Data

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

5.2.2.1. Geometric Means

For immunogenicity results of SARS-CoV-2 serum neutralizing titers, the GMTs will be computed along with associated 95% CIs. The GMTs 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 transformations of titers, calculating the 95% CI with reference to the Student's t-distribution, and then exponentiating the confidence limits.

5.2.2.2. Geometric Mean Fold Rises

GMFRs will be defined as the result after vaccination divided by the result 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 neutralization titers or antibody levels (later result minus earlier result) and exponentiating the mean. The associated 2-sided 95% CIs are obtained by constructing CIs using the Student's t-distribution for the mean difference on the natural log scale and exponentiating the confidence limits.

5.2.2.3. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

For endpoints, the missing data handling rules are described in the corresponding endpoint sections.

For the missing dates, the sponsor data standard rules for imputation will be applied (eg, partial dates for AEs will be imputed according to Pfizer standard algorithms).

6. ANALYSES AND SUMMARIES

Most of immugenicity and safety summaries will be provided by age category (20 to 64 years of age and 65 to 85 years of age) in addition to overall population.

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoints

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) 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.

[redacted]

- Reporting results: Descriptive statistics for each and any local reaction after each dose in each vaccine group will be presented by maximum severity across severity levels. Confirmed e-diary errors will be excluded from the analysis. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplementary Analyses

To support the assessment of local reactions, the following endpoints (as defined in Section 3.1.1.1) will be summarized with the same analysis time point and analysis population, analysis methodology, and appropriate reporting results. Confirmed e-diary errors will be excluded from these analyses.

- 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.

Figures:

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

6.1.1.2. Systemic Events

6.1.1.2.1. 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.
- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group will be presented by maximum severity across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

[redacted]

6.1.1.2.2. Supplementary Analyses

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

- Duration of each systemic event after 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 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days after each dose will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by severity.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 1 month after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1) and additional 3-tier approach (Section 3.1.1.4).
- Intercurrent events and missing data: Partial AE dates will be imputed using the Pfizer standard algorithm.

- Reporting results: AEs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers (Section 3.1.1.4). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the active vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[2] method will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within the SOC. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs for each vaccine group.

6.1.1.3.2. Supplementary Analyses

Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed. AESIs will also be listed.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 1 to 12 months after Dose 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 12 months after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Partial SAE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 12 months after Dose 2 will be provided for each vaccine group.

6.1.1.5. Hematology and Chemistry Parameters (for Clinical Laboratory Subset)

6.1.1.5.1. Main Analyses

- Estimands: The percentage of participants with abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 (Section 2.1).
- The percentage of participants with grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2 (Section 2.1).

[redacted]

- Analysis set: Safety population including clinical laboratory subset only (Section 4).
- Analysis time point: 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Analysis methodology: Descriptive statistics including counts and percentage (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive summary statistics will be provided including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs for each vaccine group by age category (20 to 64 years of age and 65 to 85 years of age).

6.1.2. Immunogenicity Endpoints

The statistical analysis of immunogenicity results will be primarily based on the Evaluable immunogenicity populations as defined in the protocol, Section 9.3.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

6.1.2.1. SARS-CoV-2 Neutralizing Titers

6.1.2.1.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFR from before vaccination to 1 month after Dose 2 (Section 2.1).
- Analysis set: Evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after Dose 2.
- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results (Section 5.2.2.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiated to transform results back to the original scale. Two-sided CIs will be obtained by calculating CIs using the Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits (Section 5.2.2.2).

- Intercurrent events and missing data: Titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.

- Reporting results: GMTs 1 month after Dose 2 and GMFR from before vaccination to 1 month after Dose 2 and the associated 2-sided 95% CIs.

6.1.2.1.2. Additional Exploratory Analyses

Similar analysis for SARS-CoV-2 serum neutralizing titers may be performed by baseline SARS-CoV-2 status (positive or negative). Positive SARS-CoV-2 at baseline is defined by a positive N-binding antibody result or positive NAAT result at baseline.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

6.2.1.1. SARS-CoV-2 Serum Neutralizing Titers

6.2.1.1.1. Main Analyses

- Estimands:

  - GMTs (Section 2.1).

  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).

- Analysis set: Evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: Baseline and 21 days after Dose 1; 7 and 14 days and 6, and 12 months after Dose 2.

Analysis methodology, intercurrent events and missing data, and reporting results should be referred to Section 6.1.2.1.1.

6.2.1.1.2. Additional Exploratory Analyses

Similar analysis for SARS-CoV-2 serum neutralizing titers may be performed by baseline SARS-CoV-2 status (positive or negative). Positive SARS-CoV-2 at baseline is defined positive N-binding antibody result or positive NAAT result at baseline. However, if the number of participants with baseline SARS-CoV-2 positive status is less than 10, the summary will not be performed.

6.2.1.1.3. Subgroup Analyses for Participants With/Without Confirmed COVID-19 Before Dose 2

Primary/secondary endpoints for SARS-CoV-2 serum neutralizing titer will be performed by subgroup of participants with/without confirmed COVID-19 before Dose 2) as described in Section 3.2. However, if the number of participants with confirmed COVID-19 before Dose 2 is less than 10, only listings will be displayed.

[redacted]

The definition to include participants for the subgroup analysis is described in Section 3.2.

6.3. Exploratory Endpoints

6.3.1. Immunogenicity Endpoints

6.3.1.1. SARS-CoV-2 Serum Neutralizing Titers

6.3.1.1.1. Subgroup Analyses for Participants With/Without Confirmed COVID-19 During the Study

Primary/secondary endpoints for SARS-CoV-2 serum neutralizing titer will be performed by subgroup of participants with/without confirmed COVID-19 during the study as described in Section 3.1.1. However, if the number of participants with confirmed COVID-19 during the study is less than 10, only listings will be displayed.

The definition to include participants for the subgroup analysis is described in Section 3.1.1.

6.3.1.2. SARS-CoV-2 N-Binding Antibody

- Estimands:
  - Percentage of participants with seroconversion by N-binding antibody.
- Analysis set: Participants with seroconversion with/without confirmed COVID-19 during the study in evaluable and all-available immunogenicity populations (Section 4). However, if the number of participants with confirmed COVID-19 during the study is less than 10, the summary will be performed for the participants without confirmed COVID-19 during the study in evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: Baseline and 21 days after Dose 1; 7 and 14 days and 1, 6, and 12 months after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Titers/concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. Missing data will not be imputed.
- Reporting results: Percentages of participants with seroconversion will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method) at each time point after vaccination.

[redacted]

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

6.4.1.1. Demographic Characteristics

Demographic characteristics, sex, race/racial designation, and ethnicity, will be summarized for the safety population for each vaccine group and overall.

6.4.1.2. Medical History

Each reported medical history term will be mapped to a SOC and PT according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group and overall, for the safety population.

6.4.2. Study Conduct and Participant Disposition

6.4.2.1. 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 follow-up visits (1 month after Dose 2), and who withdrew before each follow-up visit along with the reasons for withdrawal will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

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

Also, for participants who were originally randomized to BNT162b2, or participants who were originally randomized to placebo but declined BNT162b2 after unblinding, the numbers and percentages of participants who completed the follow-up visits (6-month visit and 12-month visit) and who withdrew from the study will be tabulated. For the participants who were originally randomized to placebo but received BNT162b2 after unblinding, the numbers and percentages of participants who received Dose 3 (first dose of BNT162b2) and Dose 4 (second dose of BNT162b2), who completed the telephone contact (1 month after Dose 4 and 6 month after Dose 4), and who withdrew from the study will be tabulated.

6.4.2.2. Blood Samples for Assay

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

6.4.2.3. E-Diaries

The participants who were vaccinated and completed e-diaries after each dose will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1.1 and Section 6.1.1.2, the summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary, and transmitting the e-diary for any day in the required reporting period, by received vaccine group for each dose.

The safety population will be used.

6.4.3. Study Vaccination Exposure

6.4.3.1. 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 percentages is the total number of randomized participants in the given vaccine group or overall.

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

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

For the participants who were originally randomized to placebo but received BNT162b2 after unblinding, the number and percentage of participants receiving Dose 3 (first dose of BNT162b2) and Dose 4 (second dose of BNT162b2) within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated.

6.4.4. Prior/Concomitant Vaccinations

Each prior/concomitant vaccine will be summarized according to the ATC 4th-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 will be tabulated by vaccine group. Summarization will be done for the interval between Dose 1 and 1 month after Dose 2. The safety population will be used.

6.4.5. Safety Summaries and Analyses

Local reaction, systemic event, AE, and SAE summaries and analyses are described under Primary Endpoint(s) (Section 6.1).

As safety analysis after unblinding for the purpose to be offered the opportunity to receive BNT162b2 for all participants who originally received placebo from protocol amendment 3, counts, percentages, and associated Clopper-Pearson 95% CIs of the participants reporting the following will be displayed:

- AEs and SAEs reported from Dose 1 to before unblinding (safety population).
- AEs reported after unblinding (participants who originally received BNT162b2 and participants who originally received placebo but declined BNT162b2 after unblinding).
- AEs reported after unblinding and the first dose of BNT162b2 (participants who originally received placebo and received BNT162b2 after unblinding).

[redacted]

7. ANALYSES TIMING

7.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Primary analysis: complete safety and immunogenicity data through 1 month after Dose 2 from all participants.

An interim summary at different time points may be considered to support internal decisions for additional visits and to support regulatory interactions.

The study's final analysis will be performed when all participants have completed the study and all immunogenicity and safety data are available.

7.2. Data Monitoring Committee or Other Independent Oversight Committee

An external DMC will be utilized for this study and will review cumulative unblinded safety data throughout the study in accordance with the charter.

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

8. REFERENCES

1. Agresti A. Introduction: Distributions and inference for categorical data. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

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

[redacted]

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AESI	adverse event of special interest
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BLQ	below the level of quantitation
BUN	blood urea nitrogen
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
IWR	interactive web-based response
LLOQ	lower limit of quantitation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
N	nucleoprotein
N/A	not applicable
N-binding	SARS-CoV-2 nucleoprotein–binding
NAAT	nucleic acid amplification test
non-S	nonspike protein
PRT	protocol
PT	preferred term
RBC	red blood cell
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOC	system organ class

Appendix 1. List of Abbreviations

Abbreviation	Term
SOP	standard operating procedure
ULN	upper limit of normal
WBC	white blood cell

[redacted]