Protocol C4591024

A PHASE 2b, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF VACCINE CANDIDATE BNT162b2 IN IMMUNOCOMPROMISED PARTICIPANTS ≥2 YEARS OF AGE

Statistical Analysis Plan
(SAP)

Version: 3

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PFIZER GENERAL BUSINESS
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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 09 Sep 2021	Protocol amendment 2 05 Aug 2021	N/A	N/A
2/ 06 Jun 2022	Protocol amendment 4 21 Jan 2022	To align with protocol amendment 4	• Updated the primary and exploratory endpoints for immunocompromised subjects receiving third/fourth doses of BNT162b2 in Table 2. • Updated the study design for subjects receiving a fourth dose in Section 2.2. • Updated Sections 3.1.1, 3.1.2.4, and 6 with the time points for the primary and exploratory objectives. • Added the SARS-CoV-2 objective to the additional analysis in Section 3.3.3. • Updated Section 3.4.3 with the collection visit for prior/concomitant vaccines and concomitant medications. • Updated the evaluable populations for Dose 3 and Dose 4 subjects in Section 4. • Updated Section 6.1.1.1 to include analysis sets/time points for Dose 4. • Updated Section 6.1.2.3.1 to include time points for Dose 4. • Updated Sections 6.3.1.1 and 6.3.1.2 with the GMR and GMFR time points and added an analysis for subjects with seroresponse. • Updated Section 6.3.3.2 to include time points for Dose 4. • Updated Section 6.3.3.1 to include the additional analysis for SARS-CoV-2 variants. • Updated Section 6.4 to remove the subgroup analysis for the study. • Updated Section 6.5.2.1 to include Dose 4 time points. • Updated the interim analysis section (Section 7.2) with the statistical analysis timing for subjects receiving Dose 4. • Updated Appendix 2 with surveillance times for Dose 3 and Dose 4.
3/ 24 Jul 2023	Protocol amendment 5 16 Jan 2023	To align with protocol amendment 5	• Updated the number of participants in each group based on actual recruitment figures in Section 2.2. • Updated the interim analysis section (Section 7.2) to remove the statistical analysis timing for safety and

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			immunogenicity data through 1 month after Dose 3 and to match the protocol. • Updated Section 6.3.3.1 due to limited samples. • Updated Appendix 2 to include "chills" as a COVID-19 symptom. • Deleted PBMC analysis from Table 2, Section 3.3.3, and Section 6.3.3.1 because PBMC sample collection was removed from the SoA. • Updated Section 5.2 to match the protocol. • Removed "Confirmed e-diary errors will be excluded from the analysis" from Section 6.1.2.1.1 and Section 6.1.2.2.1 to avoid confusion. • Updated Section 3.1.2.1, Section 3.1.2.2, Section 6.1.2.1, and Section 6.1.2.2 to capture the new reactogenicity analysis approach requested by the FDA.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591024. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

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

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (see Section 4 for definitions). These estimands estimate the vaccine effect in the hypothetical settings 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.

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

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

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the immune response to prophylactic BNT162b2 in participants ≥18 years of age without serological or virological evidence of past SARS-CoV-2 infection and with: • Asymptomatic CLL without treatment and undergoing observation, or CLL on BTK inhibitor or anti-CD20 monoclonal antibodies • Diagnosed with NSCLC and on chemotherapy, checkpoint inhibitors, or targeted agents for oncogene-driven tumors • Maintenance hemodialysis treatment due to end-stage renal disease • Immunomodulator therapy for an autoimmune inflammatory disorder	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each disease subset: • GMTs at 1 month after Dose 3 and Dose 4	• SARS-CoV-2 neutralizing titers
To describe the immune response to prophylactic BNT162b2 in participants ≥2 to <18 years of age without serological or virological evidence of past SARS-CoV-2 infection and either: • Are on immunomodulator therapy for an autoimmune inflammatory disorder • Are on immunosuppression therapy after solid organ transplant • Underwent bone marrow or stem cell transplant at least 6 months before enrollment	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each age group (≥2 to <5, ≥5 to <12, and ≥12 to <18 years) and disease subset: • GMTs at 1 month after Dose 3 and Dose 4	• SARS-CoV-2 neutralizing titers
To describe the safety and tolerability of prophylactic BNT162b2 in participants ≥18 years of age with: • Asymptomatic CLL without treatment and undergoing observation, or CLL on BTK inhibitor or anti-CD20 monoclonal antibodies • Diagnosed with NSCLC and on chemotherapy, checkpoint	In participants receiving at least 1 dose of study intervention in each disease subset, 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 through 1 month after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

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

Objectives	Endpoints	Estimands
inhibitors, or targeted agents for oncogene-driven tumors • Maintenance hemodialysis treatment due to end-stage renal disease • Immunomodulator therapy for an autoimmune inflammatory disorder	• AEs from Dose 3 through 1 month after Dose 3 • AEs from Dose 4 through 1 month after Dose 4 • SAEs from Dose 1 through the duration of the study	
To describe the safety and tolerability of prophylactic BNT162b2 in participants ≥2 to <18 years of age and either: • Are on immunomodulator therapy for an autoimmune inflammatory disorder • Are on immunosuppression therapy after solid organ transplant • Underwent bone marrow or stem cell transplant at least 6 months before enrollment	In participants receiving at least 1 dose of study intervention in each age group (≥2 to <5, ≥5 to <12, and ≥12 to <18 years) and disease subset, 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 through 1 month after Dose 2 • AEs from Dose 3 through 1 month after Dose 3 • AEs from Dose 4 through 1 month after Dose 4 • SAEs from Dose 1 through the duration of the study	• 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
Exploratory:	**Exploratory:**	**Exploratory:**
To further describe the immune response to prophylactic BNT162b2 in participants ≥18 years of age without serological or virological evidence of past SARS-CoV-2 infection and with: • Asymptomatic CLL without treatment and undergoing observation, or CLL on BTK inhibitor or anti-CD20 monoclonal antibodies • Diagnosed with NSCLC and on chemotherapy, checkpoint inhibitors, or targeted agents for oncogene-driven tumor • Maintenance hemodialysis treatment due to end-stage renal disease • Immunomodulator therapy for an autoimmune inflammatory disorder	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each disease subset: • GMTs at all immunogenicity blood draws • GMFRs from baseline to 1 month after Dose 2, from baseline to 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4 • Percentages of participants with seroresponse at 1 month after Dose 2, 1 month after Dose 3, at Dose 4, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers

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

Objectives	Endpoints	Estimands
To further describe the immune response to prophylactic BNT162b2 in participants ≥2 to <18 years of age without serological or virological evidence of past SARS-CoV-2 infection and either: • Are on immunomodulator therapy for an autoimmune inflammatory disorder • Are on immunosuppression therapy after solid organ transplant • Underwent bone marrow or stem cell transplant at least 6 months before enrollment	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each age group (≥2 to <5; ≥5 to <12; ≥12 to <18) and disease subset: • GMTs at all immunogenicity blood draws • GMFRs from baseline to 1 month after Dose 2, from baseline to 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4 • Percentages of participants with seroresponse at 1 month after Dose 2, 1 month after Dose 3, at Dose 4, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To further describe the immune response to prophylactic BNT162b2 in participants with and without serological or virological evidence of past SARS-CoV-2 infection	• GMTs at all immunogenicity blood draws • GMFRs from baseline to 1 month after Dose 2, from baseline to 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4 • Percentages of participants with seroresponse at 1 month after Dose 2, 1 month after Dose 3, at Dose 4, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To describe the incidence of confirmed COVID-19 among immunocompromised participants	• Incidence rate of confirmed COVID-19 per 1000 person-years of follow-up	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To characterize SARS-CoV-2 variants in the study population	• The number and percentage of each SARS-CoV-2 lineage among BNT162b2 recipients	• SARS-CoV-2 lineage determined by next-generation sequencing
To describe the incidence of MIS-C cases	• Incidence rate of confirmed MIS-C cases	• Confirmed cases as per CDC symptom criteria

2.2. Study Design

This is a Phase 2b, open-label study with BNT162b2 in immunocompromised participants ≥18 years of age treated for NSCLC or CLL, receiving hemodialysis treatment secondary to

end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder, and in immunocompromised participants ≥2 to <18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrollment. This study will evaluate the safety, tolerability, and immunogenicity of BNT162b2:

- Open-label; 4 doses, with the primary series consisting of 2 doses separated by 21 days and a third dose occurring 28 days after Dose 2. The fourth (booster) dose will occur 3 to 6 months after Dose 3. Note that the timing of the fourth dose should be determined by the investigator's discretion, considering such factors as the participant's underlying condition and level of immunosuppression, the evolving clinical literature, the COVID-19 incidence in the participant's geographic area, and the potential for increased reactogenicity with Dose 4 occurring earlier. Additionally, although more data are needed for COVID-19 vaccines, there is a risk of reduced immunogenicity and antibody persistence with a shorter interval between Dose 3 and Dose 4. Investigators are encouraged to weigh the risks and benefits for each participant and make an individualized decision on the timing of the fourth dose, provided it falls within the minimum and maximum time frames detailed above. Depending on the timing of Dose 4, participants are expected to participate for up to 14 months, with a maximum of approximately 15 months.

The dose for each of the 4 vaccinations will depend upon the age of the participant at the time of vaccination, as follows:

- For participants who are ≥12 years of age (on the day of vaccination): at a 30-µg dose level
- For participants who are ≥5 to <12 years of age (on the day of vaccination): at a 10-µg dose level
- For participants who are <5 years of age (on the day of vaccination): at a 3-µg dose level

Approximately 124 participants in total have been enrolled, with the following breakdown:

- In approximately 7 participants who are ≥18 years of age (at Visit 1) in the following groups:
    - Approximately 1 participant who is treatment-naïve with planned treatment (≥14 days) or who is receiving treatment for NSCLC
    - Approximately 0 participants receiving treatment or under observation for CLL

  - Approximately 1 participant receiving maintenance hemodialysis treatment secondary to end-stage renal disease
  - Approximately 5 participants receiving immunomodulator treatment for an autoimmune inflammatory disorder

- In approximately 117 immunocompromised participants who are <18 years of age (at Visit 1), with:
  - Approximately 37 participants: ≥2 to <5 years of age
  - Approximately 65 participants: ≥5 to <12 years of age
  - Approximately 15 participants: ≥12 to <18 years of age
- In each of the cohorts <18 years of age (at Visit 1), participants with the following immunocompromising conditions will be recruited/enrolled:
  - Immunomodulator treatment for an autoimmune inflammatory disorder (≥10 participants in each age cohort)
  - Immunomodulator treatment after solid organ transplant (≥10 participants in each age cohort)
  - Underwent bone marrow or stem cell transplant ≥6 months (182 days) before enrollment (≥10 participants in each age cohort)
- Follow-up for 6 months after Dose 4.
- Local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain) will be prompted for and collected by all participants or participants' parent(s)/legal guardians in an e-diary each day from Day 1 (the day of vaccination) through Day 7 after each administration of study intervention. AEs will be collected from the time the participant or participant's parent(s)/legal guardian provides informed consent through 1 month after Dose 2, from Dose 3 through 1 month after Dose 3, and from Dose 4 through 1 month after Dose 4. SAEs will be collected from the time of informed consent through the duration of the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

- SARS-CoV-2 neutralizing titers at 1 month after Dose 3 and 1 month after Dose 4 in participants ≥18 years of age without serological or virological evidence of past SARS-CoV-2 infection.

- SARS-CoV-2 neutralizing titers at 1 month after Dose 3 and 1 month after Dose 4 in participants ≥2 to <18 years of age without serological or virological evidence of past SARS-CoV-2 infection.

3.1.2. Primary Safety Endpoints

- Local reactions (redness, swelling, and pain at the injection site) for up to 7 days following each dose.

- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following each dose.

- AEs from Dose 1 through 1 month after Dose 2

- AEs from Dose 3 through 1 month after Dose 3

- AEs from Dose 4 through 1 month after Dose 4

- SAEs from Dose 1 through the duration of the study

3.1.2.1. 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. The e-diary entries from the participant and unplanned clinical assessments within 7 days after vaccination will be the primary data source for these events. In addition, any AEs recorded on the AE CRF that are considered local reactions within 7 days after vaccination will be consolidated with e-diary data and included in the reactogenicity report.

This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

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

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 scales in Table 4 and Table 5. 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 to the grading scales in Table 4 and Table 5.

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

If redness or swelling >14 measuring device units is reported in the reactogenicity e-diary, regardless of the participant's age, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If Grade 3 pain at the injection site 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 can classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor 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. Local Reaction Grading Scale for Participants ≥12 Years of Age (at Visit 1)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
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. For participants experiencing local reactions >14 measuring device units (>7 cm), a telephone contact should occur to determine if an unscheduled visit may be required.
b. Only an investigator or qualified designee can classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in the protocol (Section 10.2.3).

Table 5. Local Reaction Grading Scale for Participants ≥2 to <12 Years of Age (at Visit 1)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site
Redness	0.5 to 2.0 cm (1 to 4 measuring device units)	>2.0 to 7.0 cm (5 to 14 measuring device units)	>7 cm (>14 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	0.5 to 2.0 cm (1 to 4 measuring device units)	>2.0 to 7.0 cm (5 to 14 measuring device units)	>7 cm (>14 measuring device units)	Necrosis

a. For participants experiencing local reactions >14 measuring device units (>7 cm), a telephone contact should occur to determine if an unscheduled visit may be required.
b. Only an investigator or qualified designee can classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in the protocol (Section 10.2.3).

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.

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

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive. 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 dose, the end date/day for the ongoing reaction 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 after vaccination that a reaction is reported of any severity.

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, vomiting, diarrhea, headache, fatigue/tiredness, chills, 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 e-diary entries from the participant and unplanned clinical assessments within 7 days after vaccination will be the primary data source for these events. In addition, any AEs recorded on the AE CRF that are considered systemic events starting within 7 days after vaccination will be consolidated with e-diary data and included in the reactogenicity report. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event; severity level, duration, and onset day (see Section 3.1.2.1).

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.2.1).

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6. For events recorded in the AE CRF that are considered systemic events and consolidated with e-diary data, the severity will be based on the AE intensity grade recorded in the CRF.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
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.

a. For participants experiencing severe systemic events, a telephone contact should occur to determine if an unscheduled visit may be required.
b. Only an investigator or qualified designee can classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 systemic events will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in the protocol (Section 10.2.3).

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

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 7 below.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person can confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant. If a fever is reported in the AE CRF within 7 days after vaccination and no temperature is captured in the CRF, the fever will be included in the reactogenicity summary with "unknown" for temperature range.

Table 7. Scale for Fever

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

Note: Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F).

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

3.1.2.3. 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 1 month after Dose 2, from Dose 3 through 1 month after Dose 3, and from Dose 4 through 1 month after Dose 4. AEs will be categorized according to MedDRA terms.

The primary safety endpoints "AEs from Dose 1 through 1 month after Dose 2," "AEs from Dose 3 through 1 month after Dose 3," "AEs from Dose 4 through 1 month after Dose 4," and other AE endpoints will be summarized by system organ class and preferred term at the participant level.

These primary safety endpoints will be supported by summaries and listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after each dose), and AESIs (defined in Section 8.3.8 of the protocol). 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 be collected from the time the participant provides informed consent through the duration of the study. SAEs will be categorized according to MedDRA terms.

The primary safety endpoint "SAEs from Dose 1 through the duration of the study" will be summarized by system organ class and preferred term at the participant level. Additionally, the SAEs will be listed.

3.2. Secondary Endpoints

Not applicable.

3.3. Exploratory Endpoints

3.3.1. Immunogenicity Endpoints

- SARS-CoV-2 neutralizing titers at all immunogenicity blood draws

3.3.2. Efficacy Endpoints

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
- MIS-C incidence per 1000 person-years of follow-up

3.3.3. Additional Endpoints

- SARS-CoV-2 lineage determined by next-generation sequencing

3.4. Baseline 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), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

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

Medical history will be categorized according to MedDRA.

A physical examination at Visit 1 and Visit 2 will be performed according to the SoA and will evaluate any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2 of the protocol) must be reported according to the processes in Sections 8.3.1 through 8.3.3 of the protocol.

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 Visit 10.
- All current medication at baseline, including the name of the medication, start date, dose, unit, route, and frequency.
- All medications (prescription and nonprescription) given during the study, including the name of the medication, start date, stop date, dose, unit, route, and frequency.
- Nutritional supplements, including vitamins, minerals, and herbal supplements, do not need to be recorded.
- Prohibited medications listed in the protocol, Section 6.8.1, will be recorded in the CRF, to include start and stop dates, name of the medication, dose, unit, route, and frequency from the signing of the ICD through the final study visit.

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

3.5. Safety Endpoints

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety, immunogenicity, and efficacy results in the table below. For the specified criteria in each population definition, data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database, and the classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who have a signed ICD and assent (where appropriate).
Assigned to study intervention	All participants who are assigned a randomization number in the IRT system.
Dose 3 evaluable immunogenicity	All participants who 1. Are eligible; 2. Receive 3 doses of the vaccine to which they are assigned, with Dose 2 received within 19 to 42 days after Dose 1 and Dose 3 received within 28 to 189 days, inclusive, after Dose 2; 3. Have at least 1 valid and determinate immunogenicity result within an appropriate window at Visit 7 (28-42 days, inclusive, after Dose 3); and 4. Have no other important protocol deviations as determined by the clinician.
Dose 4 evaluable immunogenicity	All participants who 1. Are eligible; 2. Receive 4 doses of the vaccine to which they are assigned, with Dose 2 received within the predefined window (19-42 days, inclusive, after Dose 1), Dose 3 received within 28 to 189 days, inclusive, after Dose 2, and Dose 4 received within the predefined window (91-189 days, inclusive, after Dose 3); 3. Have at least 1 valid and determinate immunogenicity result within an appropriate window at Visit 9 (28-42 days, inclusive, after Dose 4); and 4. 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 with at least 1 valid and determinate immunogenicity result after vaccination.
Safety	All 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 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.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the corresponding 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 assigned.

The safety analyses will be based on the safety population. Participants will be summarized by vaccine group according to the study interventions participants 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.

This is an open-label study. Further details can be found in the protocol, Section 6.3. The timing for statistical analyses is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Statistical Hypothesis

There is no statistical hypothesis specified in this study. All statistical analyses will be descriptive.

5.1.2. Multiplicity Considerations

No multiplicity adjustment is needed for the study, as there is no statistical hypothesis.

5.2. General Methods

All safety and immunogenicity data will be analyzed separately for each disease subset in participants ≥18 years of age and for each disease subset in each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age). Analyses for certain cohorts may be combined if the number of participants is small. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless otherwise specified.

Missing reactogenicity e-diary data will not be imputed; missing start AE dates will be handled according to the Pfizer safety rules.

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (denoted by lowercase n), and the denominator (denoted by uppercase 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]

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

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

5.2.2.2. Geometric Mean Fold Rises

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

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

5.2.2.3. 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.

5.2.3. Analyses for Count Data

Descriptive statistics for count data are incidence rate, the numerator (number of events observed), and the denominator (total person-years of follow-up) used in the incidence rate calculation, and the 95% CIs where applicable.

The exact 95% CI for incidence rates for each group will be computed using the method of Ulm[2] based on the link between the chi-square distribution and the Poisson distribution.

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 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoints

6.1.1.1. SARS-CoV-2 Neutralizing Titers in Participants Without Serological or Virological Evidence of Past SARS-CoV-2 Infection

6.1.1.1.1. Main Analysis

- Estimand: GMTs (Section 2.1).
- Analysis sets: Dose 3 evaluable immunogenicity population, Dose 4 evaluable immunogenicity population, all-available immunogenicity population as applicable (Section 4).
- Analysis time points: 1 Month after Dose 3, 1 month after Dose 4.
- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1 in participants without serological or virological evidence of past SARS-CoV-2 infection

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

- Reporting results: GMTs and corresponding 2-sided 95% CIs will be provided for each disease subset in participants ≥18 years of age and for each disease subset in each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age).

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers for each age group and disease subset (Section 5.2.2.3).

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 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 or unplanned clinical assessment data and without reactogenicity data reported in the AE CRF throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.

- Reporting results: Descriptive statistics for each and any local reaction after each dose in each disease subset for participants ≥18 years of age and in each disease subset for each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age) will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.2.1.2. Supplementary Analyses

To support the assessment of local reactions, the following endpoints will be summarized with the same analysis time points and analysis populations as above as well as the appropriate analysis methodology and reporting results.

- 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 age group and disease subset.

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

Figures:

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

6.1.2.2. Systemic Events

6.1.2.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary or unplanned clinical assessment data and without reactogenicity events reported in the AE CRF 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 disease subset for participants ≥18 years of age and in each disease subset for each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age) will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.2.2.2. Supplementary Analyses

The following endpoints for assessment of systemic events will be summarized similarly to the assessment of local reactions per each age group and disease subset:

- 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 age group and disease subset.

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 throughout 7 days after each dose will be plotted for each age group and disease subset. The bars will be divided into severity categories to highlight the proportions of participants by severity.

6.1.2.3. Adverse Events

6.1.2.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 2, from Dose 3 through 1 month after Dose 3, and from Dose 4 through 1 month after Dose 4 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time points: From Dose 1 through 1 month after Dose 2, from Dose 3 through 1 month after Dose 3, and from Dose 4 through 1 month after Dose 4
- Analysis methodology: Descriptive statistics described in Section 5.2.1.
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates, which will be imputed using the Pfizer standard algorithm (Section 5.3).
- Reporting results: AEs will be categorized according to MedDRA terms. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will

be provided for any AEs and by each system organ class and each preferred term within system organ class for each disease subset in participants ≥18 years of age and for each disease subset in each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age).

6.1.2.3.2. Supplementary Analyses

Related AEs, severe AEs, immediate AEs (within the first 30 minutes after each dose), and AESIs (defined in Section 8.3.8 of the protocol) will also be summarized for each age group and disease subset.

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

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 the duration of the study (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through the duration of the study.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial SAE start dates, which will be imputed using the Pfizer standard algorithm (Section 5.3).
- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 through the duration of the study will be provided for each disease subset in participants ≥18 years of age and for each disease subset in each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age).

6.2. Secondary Endpoints

Not applicable.

6.3. Exploratory Endpoints

6.3.1. Immunogenicity Endpoints

6.3.1.1. SARS-CoV-2 Neutralizing Titers in Participants Without Serological or Virological Evidence of Past SARS-CoV-2 Infection

6.3.1.1.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFRs (Section 2.1).
  - Percentages of participants with seroresponse
- Analysis sets: Dose 3 evaluable immunogenicity population, Dose 4 evaluable immunogenicity population, all-available immunogenicity population as applicable (Section 4).
- Analysis time points:
  - GMT: At baseline (before Dose 1), 1 month after Dose 2, 1 month after Dose 3, at Dose 4, 1 month and 6 months after Dose 4.
  - GMFRs: From before vaccination to 1 month after Dose 2, from before vaccination to 1 month after Dose 3, from Dose 4 to 1 month after Dose 4, and from Dose 4 to 6 months after Dose 4.
  - Percentages of participants with seroresponse: 1 Month after Dose 2, 1 month after Dose 3, at Dose 4, and 1 month and 6 months after Dose 4.
- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs and the associated 2-sided CIs will be calculated as described in Section 5.2.2.2. Percentages of participants with seroresponse and the associated 2-sided Clopper-Pearson CIs will be derived as described in Section 5.2.1. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.

- Reporting results: GMTs, GMFRs, counts and percentages of participants with seroresponse, and the associated 2-sided 95% CIs will be provided for each disease subset in participants ≥18 years of age and for each disease subset in each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age) at each analysis time point.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers at each analysis time point for each age group and disease subset (Section 5.2.2.3).

6.3.1.2. SARS-CoV-2 Neutralizing Titers in Participants With and Without Serological or Virological Evidence of Past SARS-CoV-2 Infection

6.3.1.2.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFRs (Section 2.1).
  - Percentages of participants with seroresponse
- Analysis sets: Evaluable immunogenicity population, all-available immunogenicity population as applicable (Section 4).
- Analysis time points:
  - GMT: At baseline (before Dose 1), 1 month after Dose 2, 1 month after Dose 3, at Dose 4, 1 month and 6 months after Dose 4.
  - GMFRs: From before vaccination to 1 month after Dose 2, from before vaccination to 1 month after Dose 3, from Dose 4 to 1 month after Dose 4, and from Dose 4 to 6 months after Dose 4.
  - Percentages of participants with seroresponse: 1 Month after Dose 2, 1 month after Dose 3, at Dose 4, and 1 month and 6 months after Dose 4.
- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs and the associated 2-sided CIs will be calculated as described in Section 5.2.2.2. Percentages of participants with seroresponse and the associated 2-sided Clopper-Pearson CIs will be derived as described in Section 5.2.1. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline

measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

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

- Reporting results: GMTs, GMFRs, counts and percentages of participants with seroresponse, and the associated 2-sided 95% CIs will be provided for each disease subset in participants ≥18 years of age and for each disease subset in each of the younger age groups (≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age) at each analysis time point.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers at each analysis time point for each age group and disease subset (Section 5.2.2.3).

6.3.2. Efficacy Endpoints

6.3.2.1. COVID-19 Incidence per 1000 Person-Years of Follow-up Based on Central Laboratory or Locally Confirmed NAAT

6.3.2.1.1. Main Analyses

- Estimand:
  - COVID-19 incidence per 1000 person-years of follow-up (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and the exact 2-sided 95% CI based on Poisson distribution (Section 5.2.3) for confirmed COVID-19 cases. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Counts, incidence of confirmed COVID-19 cases per 1000 person-years of follow-up, the associated 2-sided 95% CIs, and Kaplan-Meier cumulative incidence curves will be provided.

6.3.2.2. MIS-C Incidence per 1000 Person-Years of Follow-up

6.3.2.2.1. Main Analyses

- Estimand:
  - MIS-C incidence per 1000 person-years of follow-up (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and the exact 2-sided 95% CI based on Poisson distribution (Section 5.2.3) for confirmed MIS-C cases. Kaplan-Meier cumulative incidence of MIS-C cases over time will be plotted.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Counts, incidence of confirmed MIS-C per 1000 person-years of follow-up, the associated 2-sided 95% CIs, and Kaplan-Meier cumulative incidence curves will be provided.

6.3.3. Additional Analysis

6.3.3.1. SARS-CoV-2 Variants

The number and percentage of each SARS-CoV-2 lineage for confirmed COVID-19 cases among BNT162b2 recipients may be reported.

6.4. Subset Analysis

No subgroup analysis will be planned for this study.

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 for each age group and disease subset and overall for the safety population and 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 each age group and disease subset 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 participants assigned to study intervention will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (Doses 1, 2, 3, and 4), who completed the follow-up visits, and who withdrew from each follow-up visit, along with the reasons for withdrawal, will be tabulated by each age group and disease subset (according to group assignment) and overall. The reasons for withdrawal will be those as specified in the database.

6.5.2.2. Blood Samples for Assay

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

6.5.2.3. Transmission of E-Diaries

The numbers and percentages 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 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 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 age group and disease subset and overall for all participants. The denominator for the percentages is the total number of participants assigned to study intervention in each age group and disease subset or overall.

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

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

6.5.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification.

For participants, 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 each age group and disease subset. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analyses

Local reaction, systemic event, AE, and SAE summaries and analyses are described under Primary Safety Endpoints (Section 6.1.2).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the safety and immunogenicity data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Statistical analyses may be carried out when the final data for the specified objectives for a particular cohort (out of the 7 cohorts; participants ≥18 years of age receiving treatment for CLL, NSCLC, end-stage renal disease, and an autoimmune inflammatory disorder; participants ≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age) are available:

- Safety and immunogenicity data through 1 month after Dose 4 from all participants within a particular cohort
- Complete safety and immunogenicity analysis after complete data are available at the end of the study

Analyses may be combined as one if the data become available around the same time.

7.3. Data Monitoring Committee

This study will use a DMC. The DMC is independent of the study team and includes a mix of internal and external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to 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

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical
BiPaP	bilevel positive airway pressure
BLQ	below the limit of quantitation
BNP	brain natriuretic peptide
BP	blood pressure
BTK	Bruton's tyrosine kinase
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CLL	chronic lymphocytic leukemia
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRF	case report form
CRP	C-reactive protein
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DMC	data monitoring committee
e-diary	electronic diary
ECMO	extracorporeal membrane oxygenation
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration (United States)
FiO_2	fraction of inspired oxygen
GI	gastrointestinal
GMFR	geometric mean fold rise
GMT	geometric mean titer
HR	heart rate
ICD	informed consent document
ICU	intensive care unit
IL-6	interleukin 6
IRT	interactive response technology
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
N/A	not applicable
N-binding	SARS-CoV-2 nucleoprotein–binding
NAAT	nucleic acid amplification test
NSCLC	non–small cell lung cancer
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SpO_2	oxygen saturation as measured by pulse oximetry
TBili	total bilirubin
ULN	upper limit of normal
WHO	World Health Organization

Appendix 2. Efficacy Assessments

In all cases, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness:

Confirmed COVID-19 definition (all participants): presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting;
- Inability to eat/poor feeding in participants <5 years of age;
- Chills.

For participants ≥12 years of age: Confirmed severe COVID-19, first definition[3]: confirmed COVID-19 and presence of at least 1 of the following:

- Admission to an ICU;
- Death;
- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths/min, HR ≥125 beats/min, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);

- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction.

For participants ≥12 years of age: Confirmed severe COVID-19, second definition[4]: confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Intubation or mechanical ventilation;
- Admission to an ICU;
- Death.

For participants <12 years of age: SARS-CoV-2–related hospitalization definition: confirmed COVID-19 and hospitalization.

For participants <12 years of age: SARS-CoV-2–related severe case definition: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness:
  - RR (breaths/min) and HR (beats/min) as shown in Table 8[5] below;
  - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg[6];
- Respiratory failure (defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg):
    - <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or requiring vasoactive drugs to maintain BP in the normal range;
- Significant acute renal failure: serum creatinine ≥2 times the ULN for age or a 2-fold increase in baseline creatinine;
- Significant GI/hepatic failure: TBili ≥4 mg/dL or ALT 2 times the ULN for age;

- Significant neurological dysfunction: Glasgow Coma Scale score ≤11 or an acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline[6];
- Admission to an ICU;
- Death.

Table 8. RR and HR, by Age, Indicative of Severe Systemic Illness

Participant Age	RR	HR
2 to <3 Years	>38	>142
3 to <4 Years	>33	>136
4 to <6 Years	>29	>131
6 to <8 Years	>27	>123
8 to <12 Years	>25	>115

Abbreviations: HR = heart rate; RR = respiratory rate.
Source: Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377(9770):1011-8.

Confirmed MIS-C definition[7]: as per the CDC MIS-C case definition:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
  - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
  - Renal (eg, acute kidney injury);
  - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
  - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);

- GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
- Dermatologic (eg, rash, mucocutaneous lesions);
- Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND

- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR
- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result;
- Current or recent exposure is established by SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms;
- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

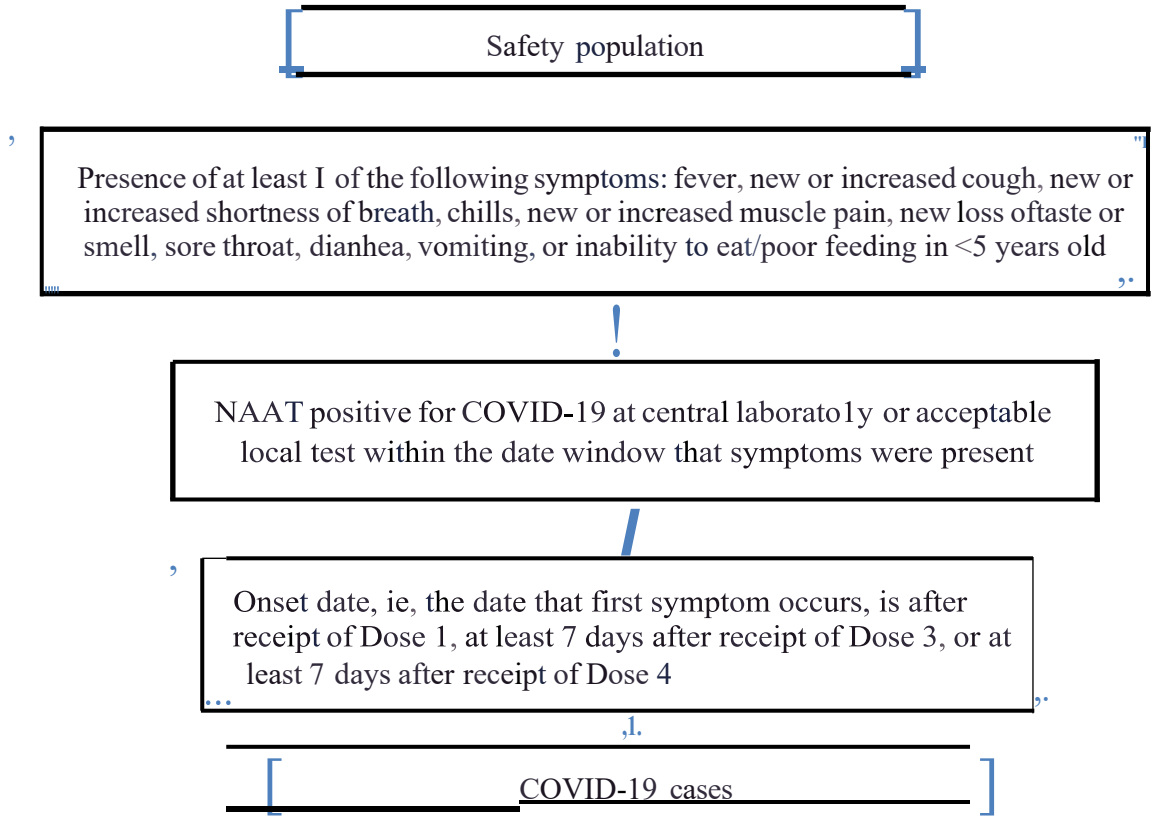
Surveillance Times

For all efficacy endpoints in this study, the start of surveillance time is Dose 1, Dose 3 + 7 days, and Dose 4 + 7 days. The end of a surveillance period for each participant is the earliest of the following events:

- When the first COVID-19 case occurs.
- When the participant's end of the study occurs due to, eg, withdrawal or death or trial completion, etc.

Flowchart

The flowcha1t for deriving COVID-19 cases after Dose 1, from 7 days after Dose 3, or from 7 days after Dose 4 for efficacy endpoints:



The central laborato1y NAAT result will be used for the case definition, unless no result is available from the central laborato1y, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpe1t Xpress SARS-CoV-2

b. Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)

c. Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

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Signed By:	Date(GMT)	Signing Capacity
PPD	25-Jul-2023 17:25:52	Final Approval