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

Study Sponsor:	BioNTech SE
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	BNT162b2 RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT Number:	2021-001290-23
ClinicalTrials.gov ID:	NCT04895982
Protocol Number:	C4591024
Phase:	2b

Brief Title Phase 2b, Open-Label Study to Evaluate Safety, Tolerability, and Immunogenicity of Vaccine Candidate BNT162b2 in Immunocompromised Participants ≥2 Years of Age

Document History

Document	Version Date
Original protocol	16 April 2021
Protocol amendment 1	24 June 2021
Protocol amendment 2	05 August 2021
Protocol amendment 3	15 September 2021
Protocol amendment 4	21 January 2022
Protocol amendment 5	13 January 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

Protocol Amendment Summary of Changes Table

Amendment 5 (13 January 2023)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Sections 1.1 Overall Design, 1.1 Number of Participants, and 4.1 Overall Design	• Updated the number of participants in each group based on actual recruitment figures	• Due to the challenging recruitment of immunocompromised participants in this study, a decision was made to stop recruiting new participants
Section 5.4 Screen Failures	• Included content from the PACL dated 25 October 2022 to clarify the definition of screen failures	• This is to align with the protocol template wording for screen failure
Sections 8.9.8 Visit 8 – Vaccination 4 (91 to 189 Days After Visit 5), 8.9.9 Visit 9 – 1-Month Follow-Up Visit (After Vaccination 4) (28 to 35 Days After Visit 8), 8.9.10 Visit 10 – 6-Month Follow-Up Visit (After Vaccination 4) (175 to 189 Days After Visit 8),	• Included content from the PACL dated 05 October 2022 to clarify the requirements for study procedures after protocol amendment 4	• This is to ensure participants can continue to perform study activities, as appropriate, if they do not consent to a fourth dose

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, and 7.1 Discontinuation of Study Intervention		
Sections 8 Study Assessments and Procedures, 9.3.4 Exploratory Endpoint(s)/Estimand(s) Analysis, and 1.3 Schedule of Activities	• Removed further blood draws for participants who have consented to PBMC sampling	• Only 1 participant to date has been enrolled in the PBMC subset due to the challenges with study enrollment overall; with too few participants to make a meaningful analysis, further collection of blood for PBMC assessment is not required
Section 8.9.8 Visit 8 – Vaccination 4 (91 to 189 Days After Visit 5)	• Included content from the PACL dated 19 May 2022 to correct a typographical error	• This is to reflect the accurate study procedures listed in Section 1.3 Schedule of Activities
Section 8.11.1 Potential COVID-19/MIS-C Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)	• Included content from the PACL dated 09 March 2022 to clarify nasal swab collection for participants in study sites in Mexico	• This is to clarify that participants will not self-collect nasal swabs in Mexico
Section 9.3.1 General Considerations	• Added the following wording: Analyses for certain cohorts may be combined if the number of participants is small	• This is in case of low recruitment
Section 9.4.1 Analysis Timing	• Streamlined the text in this section	• This is to clarify the language

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Phase 2b, Open-Label Study to Evaluate Safety, Tolerability, and Immunogenicity of Vaccine Candidate BNT162b2 in Immunocompromised Participants ≥2 Years of Age

Rationale

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~44,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate. C4591001 prohibited the enrollment of those with significantly suppressed immune function. Given that individuals with compromised immune systems (due to primary or acquired conditions, or as a result of the administration of immunosuppressant treatment) are at significant risk of morbidity and mortality due to SARS-CoV-2 infection, it is imperative that the safety, tolerability, and immune response to vaccination among this cohort be investigated. In order to obtain information regarding the safety and immunogenicity among immunosuppressed participants, representative medical conditions (and their respective treatments) have been selected for this study. Medical conditions and associated treatments have been selected on the basis of the substantial morbidity/mortality associated with COVID-19, feasible recruitment timelines, regulatory requirements, and the ability to generalize safety and immunogenicity results overall. Representative conditions for participants ≥18 years of age include NSCLC, CLL, maintenance hemodialysis treatment secondary to end-stage renal disease, and immunomodulator therapy for an autoimmune disorder. Participants ≥2 to <18 years of age with representative conditions include those with autoimmune inflammatory disorders receiving immunomodulators, those who have undergone organ transplant and are receiving maintenance antirejection medications, and those who have undergone bone marrow or stem cell transplant.

This Phase 2b study (C4591024) will evaluate safety, tolerability, and immunogenicity across all age groups based on representative medical conditions. For the participants who are ≥12 years of age, a 30-µg dose level will be used. For participants who are ≥5 to <12 years of age, a 10-µg dose level will be used. For participants who are <5 years of age, a 3-µg dose level will be used. These are the same dose levels that have been selected for participants <5 years of age and ≥5 to <12 years of age, respectively, in the Phase 2/3 C4591007 study.

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 inhibitors, or targeted agents for oncogene-driven tumors • Maintenance hemodialysis treatment due to end-stage renal disease	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 • 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

Objectives	Endpoints	Estimands
• Immunomodulator therapy for an autoimmune inflammatory disorder		
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 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 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, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers

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, and ≥12 to <18 years) 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, 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, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To describe the cell-mediated immune response, and additional humoral immune response parameters in all participants ≥12 years of age: • At baseline, 7 days after Dose 2, 1 week after Dose 3, Dose 4, and 6 months after Dose 4		
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

Overall 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 at 28 days after Dose 2. There is a fourth dose (booster) which will occur 3-6 months after Dose 3. Note that the timing of the fourth dose should be determined by the investigator's discretion, taking into account factors such 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.

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
- 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 the 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.

Number of Participants

Approximately 7 participants ≥18 years of age and 117 participants <18 years of age (approximately 124 in total) will be enrolled.

Intervention Groups and Duration

BNT162b2 will be administered to all study participants. The study will evaluate a 4-dose schedule (the first 2 doses separated by 21 days), with a third dose occurring 28 days after the second dose*. The fourth dose (booster) will occur 3-6 months after Dose 3.

For participants ≥12 years of age (on the day of vaccination): participants will receive 30 µg of BNT162b2, which is the same as that selected for Phase 3 of the pivotal vaccine study (C4591001).

For participants ≥5 to <12 years of age (on the day of vaccination): participants will receive 10 µg of BNT162b2.

For participants <5 years of age (on the day of vaccination): participants will receive 3 µg of BNT162b2.

These are the same dose levels that have been selected for participants <5 years of age and ≥5 to <12 years of age, respectively, in the Phase 2/3 C4591007 study. Participants will receive the age-appropriate dose level at each vaccination visit, as detailed above.

*Note that the timing of the fourth dose should be determined by the investigator's discretion, taking into account factors such 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 third dose, provided it falls within the minimum and maximum time frames detailed above. Depending on the timing of Dose 3 and Dose 4, participants are expected to participate for up to 14 months, with a maximum of approximately 15 months.

Data Monitoring Committee or Other Independent Oversight Committee: Yes

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

Statistical Methods

There is no statistical hypothesis in this study. All statistical analyses will be descriptive. All safety and immunogenicity data will be summarized 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.

The primary immunogenicity objectives will be evaluated descriptively by GMTs and the associated 2-sided 95% CIs for SARS-CoV-2 neutralizing titers at 1 month after Dose 3 and 1 month after Dose 4 in participants without serological or virological evidence of past SARS-CoV-2 infection.

The primary safety objectives will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs, and SAEs. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoints and the associated Clopper-Pearson 95% CIs.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed infonnation on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the paiiicipant.

Visit Number·	**1**	2	**3**	**4**	**5**	**6**	7	**8**	**9**	**10**	**Unplanned**
Visit Identifier· Abbreviations used in this table may be found in Appendix 8	**Vaxl**	**Vax2**	**7-Day Follow-Up (Aftel"Vax 2)**	**1-Month Follow-Up (Aftel"Vax 2)**	**Vax3**	**7-Day Follow-Up (Aftel"Vax 3**	**1-Month Follow-Up (Aftel"Vax 3)**	**Vax4**	**1-Month Follow-Up (Aftel" Vax4)**	**6-Month Follow-Up (After· Vax4)**	**Potential COVID-19, MIS-C Illness Visit'**
Visit Window (Days)	**Dayl**	**19 to 23 Days Aftel" Visit 1**	6 to 8 Days **Aftel"Visit 2**	28 to 35 Days **Aftel"Visit 2**	28 to 35 **Days After· Visit 2**	6 to 8 Days **After·Visit 5**	**28 to 35 Days After· Visit 5**	**91 to 189 Days After· Visit 5'**	**28 to 35 Days After· Visit 8**	**175 to 189 Days Aftel' Visit 8**	**Optimally Within3 Days Aftel' Potential COVID-19 MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic 01" TeleheaJthd**	**Clinic**	**Clinic**	**Clinic 01" Telehealthd**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic01· Telehealth**
Obtain infonued consent and assent *(if* aooropriate)	X										
Assign participant number	X										
Obtain demography and significant medical historv data	X										
Measm·e vital signse (includine:oral tempe.rature)	X	X			X			X			
Pe1fo1m a phvsical examination	X	X									
Pe1fo1m m-ine pregnancy test (only for female participants biologically capable of havine:children)	X	X			X			X			
Confum use of contraceptives *(if* annrooriate)	X	X	X	X	X	X	X	X	X		

Visit Number·	1	2	3	4	5	6	7	8	9	10	Unplanned
Visit Identifiei- Abbreviations used in this table may be found in Appendix 8	**Vaxl**	**Vax2**	**7-Day Follow-Up (Aftei-Vax 2)**	**1-Month Follow-Up (Aftei-Vax 2)**	**Vax3**	**7-Day Follow-Up (Aftei-Vax 3**	**1-Month Follow-Up (Aftei-Vax 3)**	**Vax4**	**1-Month Follow-Up (Aftei-Vax4)**	**6-Month Follow-Up (After· Vax4)**	**Potential COVID-19, MIS-C Illness Visit'**
Visit Window (Days)	**Dayl**	**19 to 23 Days Aftei-** Visit **1**	6 to 8 Days **Aftei-** Visit 2	28 to 35 Days **Aftei-Visit** 2b	28 to 35 **Days After· Visit** 2	6 to 8 Days **After·Visit 5**	**28 to 35 Days After· Visit 5**	**91 to 189 Days After· Visit 5'**	**28 to 35 Days After·** Visit 8	**175 to 189 Days Aftei-** Visit 8	**Optimally Within3 Days Aftei-Potential COVID-19, MIS-C** Illness **Onset**
Type of Visit	Clinic	Clinic	Clinic oi-**TeleheaJthd**	Clinic	Clinic	Clinic oi-**Telehealthd**	Clinic	Clinic	Clinic	Clinic	Clinic01· **Telehealth**
Collect nonstudv vaccine infonuation	X	X	X	X	X	X	X	X	X	X	
Collect medication use infonuation	X	X	X	X	X	X	X	X	X	X	X
Review temoorarv delay criteria	X	X			X			X			
Confirm eligibilitv	X	X	X	X	X	X	X	X	X	X	
Obtain studv intervention allocation	X	X			X			X			
Obtain nasal swab for detennination of ctm·ent SARS-CoV-2 status	X	X			X			X			X
Collect blood sample for immunoizenicitvf	X			X			X	X	X	X	
Collect blood samole for HLA tvoingf	X										
Administer studv intervention	X	X			X			X			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X			X			X			
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue orovisioned device if reouired	X										
Provide a thermometer and measming device	X	X									
Record systemic events at baseline in the e-diarv	X										

Visit Number·	1	2	3	4	5	6	7	8	9	10	Unplanned
Visit Identifiei- Abbreviations used in this table may be found in Appendix 8	**Vaxl**	**Vax2**	**7-Day Follow-Up (Aftei- Vax 2)**	**1-Month Follow-Up (Aftei- Vax 2)**	**Vax3**	**7-Day Follow-Up (Aftei- Vax 3**	**1-Month Follow-Up (Aftei- Vax 3)**	**Vax4**	**1-Month Follow-Up (Aftei- Vax4)**	**6-Month Follow-Up (After· Vax4)**	**Potential COVID-19, MIS-C Illness Visit'**
Visit Window (Days)	**Dayl**	**19 to 23 Days Aftei- Visit 1**	6 to 8 Days **Aftei- Visit 2**	28 to 35 Days **Aftei- Visit 2[**	28 to 35 **Days After· Visit 2**	6 to 8 Days **After·Visit 5**	**28 to 35 Days After· Visit 5**	**91 to 189 Days After· Visit 5'**	**28 to 35 Days After· Visit 8**	**175 to 189 Days Aftei- Visit 8**	**Optimally Within3 Days Aftei- Potential COVID-19, MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic oi- TelcheaJthd**	**Clinic**	**Clinic**	**Clinic oi- Telehealthd**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic 01· Telehealth**
Ensm·e the pa1ticipant/pa1ticipant's parent(s)/legal guardian has a measming device and the1mometer		**X**			**X**			**X**			
Ask the pa1ticipant/participant's parent(s)/legal guardian to complete e-diary and ensm·e that the pa1ticipant/pa1ticipant's parent(s)/legal guardian remains comfo1table with chosen e-diarv olatfo1m	**X**	**X**			**X**			**X**			
Review reactogenicity e-dia1y data (daily review is optimal dtuing the active diarv oeriod)	+---+	+---+			+---+			+---+			
Review ongoing reactogenicity e-diary svmotoms and obtain stop dates		**X**		**X**			**X**		**X**		
Collect AEsg and SAEsh	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect e-dia1y or assist the participant or participant's parent(s)/legal guardian to delete aoo										**X**	

Visit Number·	1	2	3	4	5	6	7	8	9	10	Unplanned
Visit Identifiei- Abbreviations used in this table may be found in Appendix 8	**Vaxl**	**Vax2**	**7-Day Follow-Up (Aftei- Vax 2)**	**1-Month Follow-Up (Aftei- Vax 2)**	**Vax3**	**7-Day Follow-Up (Aftei- Vax 3**	**1-Month Follow-Up (Aftei- Vax 3)**	**Vax4**	**1-Month Follow-Up (Aftei- Vax4)**	**6-Month Follow-Up (After· Vax4)**	**Potential COVID-19, MIS-C Illness Visit'**
Visit Window (Days)	**Dayl**	**19 to 23 Days Aftei- Visit 1**	**6 to 8 Days Aftei- Visit 2**	**28 to 35 Days Aftei- Visit 2[b]**	**28 to 35 Days After· Visit 2**	**6 to 8 Days After· Visit 5**	**28 to 35 Days After· Visit 5**	**91 to 189 Days After· Visit 5'**	**28 to 35 Days After· Visit 8**	**175 to 189 Days Aftei- Visit 8**	**Optimally Within3 Days Aftei- Potential COVID-19, MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic oi- TeleheaJthd**	**Clinic**	**Clinic**	**Clinic oi- Telehealthd**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic 01· Telehealth**
Collection of COVID-19/MIS-C-relatec clinical and laboratory infonuation (includinizlocal diaonosis)											**X**

Abbreviations: app = application; COVID-19 = coronavims disease 2019; CRF = case report form; DMC = data monitoring committee; HLA = human leukocyte antigen; MIS-C = multisystem inflammatory syndrome in children; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = severe acute respiratory syndrome coronavims 2.

a. Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
b. Visit 4 and Visit 5 are expected to occur on the same day. All visit procedures should be conducted in consecutive order and duplicative procedures listed in Visit 4 and Visit 5 not be done.
c. The timing of Dose 4 should be detennined by the investigator's discretion, taking into account factors such as the participant's underlying condition and level of immunosuppression, the evolving clinical literature, the COVID-19 incidence in the pa1ticipant's geographic area, the potential for increased reactogenicity, and the risk of reduced immunogenicity and antibody persistence with a shorter interval between Dose 3 and Dose 4.
d. For pruticipants not in the PBMC collection subset, this visit will be a telehealth visit.
e. Height and weight will be collected only at Visit 1.
f. Immunogenicity blood draws will be taken for all pa1ticipants, with the volume dependent on pa1ticipant age at the visit. Breakdown of blood draw by age is referenced in Table 1 (Section 8) (Note: If the participant does not receive Dose 4 ofBNT162b2, this blood draw is not required, and Visits 8, 9, and 10 may be conducted via telehealth).
g. AEs will be collected from info1med 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. In addition, any AEs occun-ing up to 48 hours after blood draw and nasal swab collection must be recorded (see Section 8.3.1). Note: Symptoms that trigger potential COVID-19/MIS-C illness visits (Section 8.11) are expected endpoints and should not be recorded as AEs. These data will be captured only on relevant illness pages of the CRF.
h. Refer to Section 8.3.1 for the time period for collecting SAEs.

2. INTRODUCTION

BNT162b2 is an RNA-based COVID-19 vaccine that is currently being investigated for the prevention of COVID-19 in individuals ≥6 months of age. On 02 December 2020, the MHRA in the UK granted a temporary authorization. On 11 December 2020, the US FDA issued an EUA for use in individuals 16 years of age and older. Other countries have also granted EUA (eg, Canada, Mexico, Bahrain), and Pfizer and BioNTech are anticipating further regulatory decisions in other countries.

2.1. Study Rationale

Study C4591001 (NCT04368728) is an ongoing Phase 1/2/3 trial in ~44,000 participants designed to generate safety, tolerability, immunogenicity, and efficacy data from a novel RNA-based vaccine candidate. C4591001 prohibited the enrollment of those with significantly suppressed immune function. Given that individuals with compromised immune systems (due to primary or acquired conditions, or as a result of the administration of immunosuppressant treatment) are at significant risk of morbidity and mortality due to SARS-CoV-2 infection, it is imperative that the safety, tolerability, and immune response to vaccination among this cohort be investigated. In order to obtain information regarding the safety and immunogenicity among immunosuppressed participants, representative medical conditions (and their respective treatments) were selected for cohort enrollment. The medical conditions and associated treatments selected accounted for morbidity/mortality associated with COVID-19, feasible recruitment timelines, regulatory requirements, and the ability to generalize safety and immunogenicity results overall. Representative conditions for participants ≥18 years of age include NSCLC, CLL, hemodialysis treatment secondary to end-stage renal disease, or immunomodulator therapy for an autoimmune inflammatory disorder. Participants ≥2 to <18 years of age with representative conditions include those with autoimmune inflammatory disorders receiving immunomodulators, those who have undergone organ transplant and are receiving maintenance antirejection modulators, and those who have undergone bone marrow or stem cell transplant.

This Phase 2b study (C4591024) will evaluate safety, tolerability, and immunogenicity across all age groups based on representative medical conditions and utilizing a primary vaccination series of 3 doses followed by a fourth booster dose. For the participants who are ≥12 years of age, a 30-µg dose level will be used. For participants who are ≥5 to <12 years of age, a 10-µg dose level will be used. For participants who are <5 years of age, a 3-µg dose level will be used. These are the same dose levels that have been selected for participants <5 years of age and ≥5 to <12 years of age, respectively, in the Phase 2/3 C4591007 study.

2.2. Background

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. In January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020.[1] On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO

officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19).[1] On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which continues to spread globally.[2]

Study C4591001 is currently being conducted in a heterogeneous study population: relatively healthy eligible participants who are ≥12 years of age, including those participants with stable chronic medical conditions, including HIV-, HCV-, and HBV-positive participants. A younger healthy population (≥6 months through 11 years of age) is being enrolled in a separate study (C4591007), and a study is in progress in pregnant women (C4591015). Study C4591001 consists of 2 parts: a completed Phase 1 part, which identified the preferred vaccine candidate (BNT162b1 or BNT162b2) and dose level (10 µg, 20 µg, 30 µg, or 100 µg [for BNT162b1]); and an ongoing Phase 2/3 part: an expanded-cohort portion to review both safety and efficacy among recipients of the selected vaccine candidate (BNT162b2). BNT162b2 was selected from the Phase 1 part of this study based on its overall safety, tolerability, and immunogenicity. In mid-November 2020, an analysis of 36,621 participants randomized 1:1 to vaccine or placebo demonstrated 8 infections in the vaccine group and 162 infections in the placebo group, resulting in a VE of 95% in preventing confirmed COVID-19, at least 7 days after receiving 2 doses. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, sexes, racial and ethnic groups, and participants, with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection.[3]

Safety data from approximately 38,000 participants at least 16 years of age, randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose, suggest a favorable safety profile. Available safety data from all participants enrolled through 14 November 2020 (N=43,252) were consistent with the safety profile demonstrated in the initial 38,000 participants.[3]

The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%); severe adverse reactions occurred in 0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). The frequency of SAEs was low (<0.5%), without meaningful imbalances between study arms. Among nonserious unsolicited AEs, there was a numerical imbalance of 4 cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, though the 4 cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between vaccine groups for specific categories of nonserious AEs (including other neurologic, neuroinflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups,

sexes, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.[3]

Regarding systemic events, 17% of the 18- to 55-year age group and 8% of those in the 65- to 85-year age group reported fever (≥38.0°C to 38.9°C) after the second dose of 30 µg of BNT162b2. Severe systemic events (fatigue, headache, chills, muscle pain, and joint pain) were reported in small numbers of younger recipients of this vaccine candidate, but no severe systemic events were reported in older recipients, and there were no Grade 4 systemic events reported.[4]

The Phase 2/3 portion of C4591001 was initiated in 18- to 85-year-old adults but was amended in September 2020 to include participants ≥16 years of age. It is intended that a minimum of 40% of participants will be in the >55-year stratum.

There are 2 primary efficacy endpoints in the Phase 2/3 part of the C4591001 study. The first is to evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination and the second is to evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants regardless of evidence of infection before vaccination. Cases of COVID-19 are defined by the presence of specified symptoms plus an NAAT for SARS-CoV-2 at least 7 days following the second dose of vaccine. Effectiveness in 12- to 15-year-old participants will be inferred by immune noninferiority to 16- to 25-year-old participants based on SARS-CoV-2–neutralizing GMTs.

MIS-C, an emerging condition that appears to be temporally related to recent exposure to SARS-CoV-2, has been described and frequently requires ICU admission, and may have a fatal outcome.[5,6] MIS-C is a febrile hyperinflammatory condition with frequent evidence of cardiac damage and dermatologic, mucocutaneous, and GI features.[6] The syndrome appears to have some overlap with Kawasaki disease shock syndrome.[7,8] Compared with Kawasaki disease, patients with MIS-C are older, have more cardiac injury, and are more likely to be Black, Hispanic, or of South Asian descent.[9] As of 29 June 2020, approximately 1000 cases had been reported.[9] As of 29 July 2020, a total of 570 cases were reported in the US to the CDC. Of these, 86.0% involved 4 or more organ systems, 63.9% of patients required ICU admission, and severe complications included cardiac dysfunction (40.6%), shock (35.4%), myocarditis (22.8%), coronary artery dilation or aneurysm (18.6%), and acute kidney injury (18.4%).[10] Death rates of 2% to 4% have been reported.[9] MIS-C has been reported in many countries throughout North America, Europe, Asia, and Latin America,[11] including the US,[5,6] Italy,[12] and France.[13] The US currently has the most reported cases globally, with the number of confirmed cases continuing to rise globally. As of 12 March 2021, there are currently no licensed vaccines or effective antiviral drugs to prevent SARS-CoV-2 infections or the disease it causes, COVID-19.[14]

2.2.1. Clinical Overview

Prior to this study, clinical data from BNT162b2 trials established a favorable safety profile characterized by mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to >19,000 people (as of the publication on 31 December 2020)[15] in clinical trials at the 30-µg dose level using a 2-dose schedule since the C4591001 Phase 1/2/3 study started in the US and other countries. BNT162b2 was also evaluated in the BNT162-01 study conducted in Germany by BioNTech, at dose levels between 1 µg and 30 µg.[16]

The Phase 1 study population included healthy participants 18 to 55 years and 65 to 85 years of age. Enrollment in C4591001 Phase 1 is complete and, although follow-up continues, the available safety data from Phase 1 participants in Study C4591001 show that BNT162b2 reactogenicity, AEs, and laboratory results were consistent with those commonly associated with vaccination. The observed reactogenicity was generally mild or moderate (primarily pain at the injection site) and short-lived. The local reactions tended to be more frequent after Dose 2. There was no redness or swelling reported by participants in the 65- to 85-year age group who received BNT162b2.[4]

No unexpected AEs or SAEs were reported. Through 1 month after receipt of the second vaccination, AEs that were considered by investigators to be related to the study intervention were reported in 25% of participants 18 to 55 years of age who received 30 µg of BNT162b2; no AEs were reported by the older population who received the same dose.[4] The available immunogenicity data from Phase 1 participants show that BNT162b2 induced a robust IgG-binding response to S1 and SARS-CoV-2 neutralizing response. Immunogenicity also substantially increased following Dose 2 of the vaccine. BNT162b2 induces a strong antigen-specific Th1-skewed CD4+ response and a strong antigen-specific CD8+ response.

The Phase 2/3 portion of C4591001 is ongoing in participants ≥12 years of age. The primary safety objective includes definition of the safety profile of prophylactic BNT162b2 as measured by solicited local reactions and systemic events captured via e-diary within 7 days after each vaccination, AEs, and SAEs.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19, which places immunocompromised individuals at higher risk for developing severe disease from infection. At the time of initiation of this study, accumulating data from ongoing human clinical trials, and use of BNT162b2 under the EUA in Europe and the US, demonstrated an acceptable safety and tolerability profile. In addition, available nonclinical data and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this PASS clinical study. This interventional study is designated as a PASS, identified as Category 3 in the EU RMP, conducted as a Conditional Marketing Approval commitment to

EMA and to Swissmedic, and an EUA commitment to the US FDA and to numerous other health authorities under respective national emergency use legislation.

The Phase 2/3 portion of the C4591001 study has reached the final efficacy analysis and demonstrates that BNT162b2 is effective, with 95% observed VE, against COVID-19 among individuals 16 years of age and older. No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 through 17 years of age were enrolled in the Phase 3 trial, safety data for this age group are limited. However, available data are consistent with the safety profile in the adult population, and it is biologically reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 12 through 17 years. The potential risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. Safety evaluation is ongoing; however, ~19,000 participants as of October 2020 have safety data available for at least 2 months of follow-up after Dose 2.[15] BNT162b2 had an overall favorable safety profile. BNT162b2 recipients reported more reactogenicity events compared to placebo recipients. In general, local reactions were mostly mild to moderate in severity and resolved within 1 to 2 days after onset. Severe fatigue was reported in 3.8% of BNT162b2 recipients; however, these events were transient. Few participants in either group had severe AEs, SAEs, or AEs leading to withdrawal from the study.[15]

More detailed information about the known and expected benefits and risks, reasonably expected AEs of BNT162b2, and the currently available safety and immunogenicity data may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): BNT162b2 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[17]	The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Study clinicians will closely monitor participants for severe reactions. In addition, investigators will contact participants or participants' parent(s)/legal guardians and conduct unscheduled visits for any reported severe local reactions or severe systemic events.
Unknown or unexpected AEs with a novel vaccine in an immunocompromised population.	Accumulating safety data from ongoing clinical studies have shown an acceptable safety profile.	Participants will be observed for a minimum of 30 minutes after vaccination to assess for immediate AEs. A DMC will be used throughout the study to review all safety data. The study team will perform ongoing clinical/safety data review of AEs and SAEs.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with RSV, feline coronavirus, and Dengue virus vaccines	Eligibility criteria will exclude any participants who have had a previous clinical (signs/symptoms only) or microbiological (signs/symptoms and positive SARS-CoV-2 NAAT result) diagnosis of COVID-19. This will minimize the low risk of potential disease enhancement and ensure that the immune response evaluated in the study is not impacted by serological changes due to previous COVID-19 disease. Temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 neutralizing titers.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
MIS-C.	Febrile hyperinflammatory condition with multisystem (≥2) organ involvement as defined in Section 8.1.	MIS-C will be prospectively collected as a potential for COVID-19/MIS-C illness visits for the duration of study participation.
Potential for worsening disease in immunocompromised participants following vaccination.	There are no ongoing COVID-19 vaccine studies studying immunocompromised participants; therefore, the potential for worsening immunocompromised disease following vaccination is unknown.	A DMC will be used throughout the study to review all safety data. AEs will be actively solicited to identify and document worsening disease. Pfizer will continue to monitor surveillance of data for BNT162b2 for emerging data.
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: The estimated rate is 5.0 per million doses administered. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.12.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant or participant's parent(s)/legal guardian obtaining a nasal swab from the participant.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood sample.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of an efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with BNT162b2 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to participants.

3. 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

Objectives	Endpoints	Estimands
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 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 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 • 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
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 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, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers

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, baseline 1 month after Dose 3, and from Dose 4 to 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, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To describe the cell-mediated immune response, and additional humoral immune response parameters in all participants ≥12 years of age: • At baseline, 7 days after Dose 2, 1 week after Dose 3, Dose 4, and 6 months after Dose 4		
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

4. STUDY DESIGN

4.1. Overall 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 at 28 days after Dose 2. There is a fourth dose (booster) which will occur 3-6 months after Dose 3. Note that the timing of the fourth dose should be determined by the investigator's discretion, taking into account factors such 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 third 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.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms as detailed in Section 8.11, a COVID-19/MIS-C illness visit will occur. As part of these visits, nasal swab samples will be taken for RT-PCR as well as recording of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis).

4.2.1. Diversity of Study Population

This study will recruit participants with disease states that may disproportionately impact certain race and ethnic populations. To the extent possible, proactive recruitment attempts will be made to enroll participants so that the overall study demographic profile approximates the general population distribution of characteristics shown below:

Race	**US Census Data[18] Target for C4591024**
Black or African American	13.4%
Asian	5.9%
American Indian or Alaska Native	1.3%
Native Hawaiian or other Pacific Islander	0.2%
White	76.3%
Ethnicity	**US Census Data Target for C4591024**
Hispanic or Latino(a) or of Spanish origin	18.5%

4.3. Justification for Dose

BNT162b2 will be administered to all study participants. The study will evaluate a 3-dose schedule (the first 2 doses separated by 21 days), with a third dose occurring at 28 days after the second dose. The fourth dose (booster) will occur 3-6 months after Dose 3*.

For participants ≥12 years of age (on the day of vaccination): participants will receive 30 µg of BNT162b2, which is the same as the dose selected for Phase 3 of the pivotal vaccine study (C4591001).

For participants ≥5 to <12 years of age (on the day of vaccination): participants will receive 10 µg of BNT162b2.

For participants <5 years of age (on the day of vaccination): participants will receive 3 µg of BNT162b2.

These are the same dose levels that have been selected for participants <5 years of age and ≥5 to <12 years of age, respectively, in the Phase 2/3 C4591007 study. Participants will receive the age-appropriate dose at each vaccination visit.

*Note that the timing of the fourth dose should be determined by the investigator's discretion, taking into account factors such 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.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreener for study recruitment purposes will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Note: "Enrolled" means a participant's or participant's parent(s)/legal guardian's (where applicable) agreement for the participant to participate in a clinical study following completion of the informed consent process. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants who are ≥2 years of age at the time of enrollment (Visit 1).

2. Participants or participants' parent(s)/legal guardians, as age appropriate, who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Life expectancy ≥12 months (365 days) in the opinion of the investigator at enrollment (Visit 1).

4. Participants or participants' parent(s)/legal guardians, as age appropriate, who are able to be contacted by telephone throughout the study period.

5. Female participant of childbearing potential or male participant able to father children who is willing to use a highly effective method of contraception as outlined in this protocol for at least 28 days after the last dose of study intervention if at risk of pregnancy with her/his partner; or female participant not of childbearing potential or male participant not able to father children.

Refer to Appendix 3 for reproductive criteria for male (Section 10.3.1) and female (Section 10.3.2) participants.

Type of Participant and Disease Characteristics:

6. Participants who are immunocompromised by virtue of the following:

- Having known NSCLC **and is ≥18 years of age** with at least 1 of the following:
  - Who received chemotherapy at least 2 weeks (14 days) before enrollment (or is treatment naïve), and is not expected to receive chemotherapy within at least 2 weeks (14 days) after dose administration; and/or
  - Receiving checkpoint inhibitor treatment (PD-1/PD-L1 inhibitor, CTLA-4 inhibitor) and has undergone at least 1 treatment cycle prior to enrollment (at Visit 1); or
  - Receiving targeted drug therapy treatment (EGFR, ALK, ROS1, BRAF, RET, MET, NTRK inhibitors) and has undergone at least 1 treatment cycle prior to enrollment (at Visit 1); or
- Having known CLL **and is ≥18 years of age** with at least 1 of the following:
  - Has asymptomatic disease (eg, Rai stage <3, Binet stage A or B) and is undergoing observation and does not receive any treatment for CLL; or
  - Receiving B-cell inhibitory monoclonal antibody treatment (anti-CD20) and has received at least 3 cycles prior to enrollment; and/or
  - Receives a BTK inhibitor, PI3K inhibitor, or BCL-2 inhibitor

OR

- Is currently undergoing maintenance hemodialysis treatment secondary to end-stage renal disease **and is ≥18 years of age**

OR

- Is on active immunomodulator therapy (eg, TNFα inhibitor, tofacitinib or MTX) for an autoimmune inflammatory disorder (eg, inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, and inflammatory bowel disease, such as ulcerative colitis and Crohn's disease) at a stable* dose

  ***Stable dose is defined as receiving the same dose for at least 3 months (84 days) with no changes in the 28 days prior to Visit 1.**

OR

- Receiving a solid organ transplant at least 3 months (84 days) prior to enrollment (Visit 1) and with no acute rejection episodes within 2 months (60 days) prior to enrollment (Visit 1), **and is ≥2 to <18 years of age**

OR

- Has had an autologous or allogenic bone marrow or stem cell transplant at least 6 months (182 days) prior to enrollment (Visit 1), with adequate immune reconstitution for immunization, in the investigator's opinion, **and is ≥2 to <18 years of age**

Informed Consent and Assent (as Appropriate):

7. The participant or participant's parent(s)/legal guardian is capable of giving signed informed consent, and assent (as appropriate), as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. The investigator, or a person designated by the investigator, will obtain written informed consent (and assent, as appropriate) from each study participant or participant's parent(s)/legal guardian (as defined in Appendix 1) before any study-specific activity is performed. All parent(s)/legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent (and assent, as appropriate) document(s).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Past clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19, or a past clinical diagnosis of MIS-C.

2. Participants with active GVHD, transplant rejection, or PTLD, or participants who have had treatment for these conditions within 3 months (84 days) prior to study enrollment (Visit 1).

3. Participants <18 years of age whose weight is less than the 5th percentile of age-adjusted ideal body weight.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

5. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

7. Participant who is pregnant or breastfeeding.

8. Participants who may be ineligible because of the number of phlebotomy assessments during this study, in the opinion of the investigator.

9. Participants who do not have adequate deltoid muscle mass to allow intramuscular vaccination, in the opinion of the investigator.

Prior/Concomitant Therapy:

10. Previous vaccination with any coronavirus vaccine.

11. Ongoing, or history of, treatment with blood/plasma products or immunoglobulins within 3 months (84 days) prior to Dose 1 or planned receipt of these medications prior to Dose 4.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

13. Previous participation in other studies involving study intervention containing LNPs.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

14. Participants who are direct descendants (child or grandchild) of investigational site staff members or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

15. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 3, Section 10.3.4) and will confirm that the participant has been instructed in its consistent and correct use.

At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met:

1. Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that, in the judgment of the investigator, could represent a potential COVID-19 illness:

    - New or increased cough;
    - New or increased shortness of breath;
    - Chills;
    - New or increased muscle pain;

- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting;
- Inability to eat/poor feeding in participants <5 years of age.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol. For the purposes of this protocol, study intervention refers to BNT162b2. This study will evaluate a 4-dose schedule of BNT162b2 (the first 2 doses separated by 21 days), with a third dose occurring a 28 days after Dose 2 for active immunization against COVID-19. A fourth dose will occur 3-6 months after Dose 3*. Participants will receive the age-appropriate dose level at each vaccination visit. The vaccine will be administered to all study participants.

For participants ≥12 years of age (on the day of vaccination): participants will receive 30 µg of BNT162b2, which is the same as the dose selected for Phase 3 of the pivotal vaccine study (C4591001).

For participants ≥5 to <12 years of age (on the day of vaccination): participants will receive 10 µg of BNT162b2.

For participants <5 years of age (on the day of vaccination): participants will receive 3 µg of BNT162b2.

These are the same dose levels that have been selected for participants <5 years of age and ≥5 to <12 years of age, respectively, in the Phase 2/3 C4591007 study. Participants will receive the age-appropriate dose level at each vaccination visit.

*Note that the timing of the fourth dose should be determined by the investigator's discretion, taking into account factors such 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.

6.1. Study Intervention(s) Administered

Study Intervention	
Intervention Name	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)
Type	Vaccine
Dose Formulation	modRNA
Unit Dose Strength(s)	250 µg/0.5 mL
Dosage Level(s)	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 ≥12 years of age (on the day of vaccination): 30 µg For participants ≥5 to <12 years of age (on the day of vaccination): 10 µg For participants <5 years of age (on the day of vaccination): 3 µg
Route of Administration	Intramuscular injection
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement.

6.1.1. Administration

Participants will receive 1 dose of study intervention at each vaccination visit (Visits 1, 2, 5, and 8) in accordance with the study's SoA. Full details are described in the IP manual.

Study intervention should be administered intramuscularly into the mid-deltoid muscle, preferably of the nondominant arm.

Standard vaccination practices must be observed, and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer's designated support team upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer's designated support team provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention once diluted.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by a medically qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse

practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

The investigator's knowledge of the study intervention should not influence the decision to enroll a participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

Not applicable to this study.

6.6. Continued Access to Study Intervention After the End of the Study

No intervention will be provided to study participants at the end of their study participation.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

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

- Any vaccinations received from 28 days prior to study enrollment until Visit 10.
- All current medication at baseline, to include name of the medication, start date, dose, unit, route, and frequency.
- All medications (prescription and nonprescription) given during the study, to include 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.

6.8.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care, including for the treatment of COVID-19.

Based on the CDC guidelines, as of June 2021, there is no prohibition of concomitant administration of COVID-19 vaccines and other licensed vaccines. However, it is important to note that while the study does not mandate a delay between administration of licensed recommended vaccines and BNT162b2, timing of these vaccinations should be based on local practice, participant risk of vaccine-preventable disease, and the reactogenicity profiles of the vaccines under consideration.

Ongoing, or history of, treatment with blood/plasma products or immunoglobulins within 3 months (84 days) prior to Dose 1 or planned receipt of these medications prior to subsequent doses is prohibited.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.8.2. Permitted During the Study

Oral corticosteroids, stable MTX, and NSAIDs are permitted.

For participants receiving MTX therapy, stable is defined as receiving MTX for at least 3 months (84 days) prior to Day 1 with no dose changes in the 28 days prior to Day 1, and not exceeding a dose of 25 mg/week.

For participants not receiving MTX therapy, treatment with MTX must have been stopped at least 3 months (84 days) prior to Day 1 and not be expected to be initiated prior to Dose 4.

It is permitted to alter the timing of immunomodulator administration before and after vaccination with BNT162b2 according to local guidelines.

Medication other than that described as prohibited in Section 6.8.1 required for treatment of preexisting conditions or acute illness is permitted.

Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 3).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: AEs warranting discontinuation; safety concern; participant's or participant's parent(s)/legal guardian's request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria or meeting 1 or more exclusion criteria*). In general, unless the investigator considers it unsafe to administer Dose 2 (or subsequent doses), or the participant does not wish to receive it, it is preferred that Dose 2 (or subsequent doses) be administered and the participant followed for safety throughout the study.

*After Vaccination 1, a positive SARS-CoV-2 NAAT result without symptoms or a COVID-19 diagnosis (signs/symptoms only or signs/symptoms and a positive SARS-CoV-2 NAAT result) should not result in discontinuation of study intervention. If study intervention (Dose 2, Dose 3, or Dose 4) has been delayed per Section 5.5, because of febrile or other acute illness (Item 1 in the list in Section 5.5), and the investigator later diagnoses the signs

and symptoms as COVID-19 (with or without a positive SARS-CoV-2 NAAT result), the participant should not be discontinued from any further doses of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, postvaccination study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her or his/her parent(s)/legal guardian's (as applicable) own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant or participant's parent(s)/legal guardian. All attempts to contact the participant or participant's parent(s)/legal guardian and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she or the participant's parent(s)/legal guardian may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant or the participant's parent(s)/legal guardian withdraws the participant from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants or participants' parent(s)/legal guardians who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant or participant's parent(s)/legal guardian specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants or participants' parent(s)/legal guardians should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or postvaccination study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and he or she, or the participant's parent(s)/legal guardian, is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant or a participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible. Counsel the participant or a participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant or a participant's parent(s)/legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant or the participant's parent(s)/legal guardian continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD and assent (where appropriate) before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for participants, dependent on their age (at Visit 1), is referenced in Table 1. This consists of blood samples for immunogenicity and additional blood collection for isolation of PBMCs. The actual collection times of blood sampling may change.

Additional blood draws for the purpose of PBMC assessment will not be collected for any participant.

Table 1. Blood Sampling Volumes per Assessment, by Age Group

	For Immunogenicity Assessments[a]	For PBMC Assessment[b]/HLA Typing	Approximate Total
≥2 to <5 Years of age	~5 mL	N/A	~30 mL
≥5 to <12 Years of age	~10 mL	N/A	~60 mL
≥12 to <18 Years of age	~20 mL	~20 mL/~5 mL	~225 mL
≥18 Years of age	~20 mL	~100 mL/~5 mL	~625 mL

Abbreviations: HLA = human leukocyte antigen; N/A = not applicable; PBMC = peripheral blood mononuclear cell; SoA = schedule of activities.
Note: Blood draw volumes are dependent on the participant's age at Visit 1, which will be the sampling volume for that participant throughout the study.
a. Immunogenicity assessments apply to visits as shown in the SoA.
b. PBMC assessments will be conducted on a subset of participants ≥12 years of age, with 1 blood draw (5 mL) for HLA typing at Visit 1.

8.1. Efficacy and/or Immunogenicity Assessments

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 serum neutralization assay
- Roche Elecsys Anti-SARS-CoV-2, an ECLIA for the presence or absence of SARS-CoV-2 N-binding antibodies

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory. Additional exploratory assays to measure immune responses may be performed, with analyses described in the SAP.

Surveillance for potential cases of COVID-19 will occur throughout a participant's involvement in the study. If, at any time, a participant develops acute illness or symptoms as detailed in Section 8.11, for the purposes of the study he or she will be considered to potentially have a COVID-19 illness. In this circumstance, the participant or participant's parent(s)/legal guardian should contact the site, and an in-person or telehealth visit should occur. A potential COVID-19/MIS-C illness visit will be initiated if, in the opinion of the investigator, an illness visit is warranted. If a COVID-19 illness visit occurs, assessments should be conducted as specified in the SoA. The assessments will include collection of a nasal swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid; FDA-approved under EUA) or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.11) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

One definition of a SARS-CoV-2–related case, and 2 definitions of SARS-CoV-2–related severe cases, will be considered (for all, 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).

8.1.1. SARS-CoV-2–Related Cases

COVID-19 Definitions:

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.

For participants ≥12 years of age: Confirmed severe COVID-19, first definition[19]: 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[20]: 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 2[21] (below);
  - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg[22];
- 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 ULN for age or 2-fold increase in baseline creatinine;

- Significant GI/hepatic failure: TBili ≥4 mg/dL or ALT 2 times ULN for age;
- Significant neurological dysfunction: Glasgow Coma Scale score ≤11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline[22];
- Admission to an ICU;
- Death.

Table 2. 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 = heat 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.

8.1.2. Multisystem Inflammatory Syndrome in Children

Confirmed MIS-C definition[23]: 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.

8.1.3. Immunogenicity

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay to establish immune responses to prefusion spike glycoprotein
- N-binding antibody assay to establish prior serological exposure to SARS-CoV-2

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

8.1.4. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better

understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained, and no testing of the participant's DNA is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation and HLA typing.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at their first visit to establish a baseline. In addition, a baseline assessment of fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain over the previous week will be recorded in the e-diary. Significant medical history and observations from any physical examination will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 30 minutes after vaccination will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever) that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.4.

8.2.1. Physical Examinations

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) must be reported according to the processes in Sections 8.3.1 through 8.3.3.

8.2.2. Vital Signs

Height, weight, oral temperature, and pulse rate will be assessed in all participants. BP will be assessed in participants ≥5 years of age (at Visit 1). Vital signs will be collected at time points specified in the SoA.

Seated BP and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used if an automated device is not available or is deemed necessary by the investigator.

BP and pulse rate measurements are best conducted when preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.2.4. Electronic Diary

Prior to vaccination on Day 1, a baseline assessment of fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain will be recorded in the e-diary.

For participants <18 years of age, their parent(s)/legal guardian may complete the e-diary on their behalf.

Participants or the participants' parent(s)/legal guardians will be required to complete a reactogenicity e-diary through an app installed on a provisioned device or on the participant's own personal device. All participants or the participants' parent(s)/legal guardians will be asked to monitor and record local reactions, systemic events, and antipyretic medication use for 7 days from the day of administration of the study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions or systemic events on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[17]

8.2.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardians will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant or his or her parent(s)/legal guardian will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) for the first 7 days following vaccination (Days 1 through 7), and then categorized during analysis as absent, mild, moderate, or severe based on the grading scales in Table 3 and 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 for participants ≥2 to <12 years of age as absent, mild, moderate, or severe according to the grading scale in Table 4. Pain at the injection site will be assessed for all participants ≥12 years of age according to the grading scale in Table 3.

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 3. 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 Section 10.2.3.

Table 4. 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 Section 10.2.3.

8.2.4.3. Systemic Events

During the reactogenicity e-diary reporting period, participants or participants' parent(s)/legal guardians will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed as absent, mild, moderate, or severe according to the grading scale in Table 5.

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

Table 5. Systemic Event Grading Scale for All Study Participants

	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

Table 5. Systemic Event Grading Scale for All Study Participants

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (Grade 4)[b]
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 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 Section 10.2.3.

8.2.4.4. Fever

In order to record information on fever, a thermometer will be given to participants or participants' parent(s)/legal guardians with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening, daily, during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection period when fever is suspected. Fever is defined as an oral temperature ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 6 during analysis.

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.

Table 6. Scale for Fever

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

8.2.4.5. Surveillance of Events That Could Represent Enhanced COVID-19 Disease

As this is a sponsor open-label study, the sponsor will conduct unblinded reviews of the data during the study, including for the purpose of safety assessment.

Participants will be surveilled for potential COVID-19/MIS-C illness from Visit 1 onwards. Participants or participants' parent(s)/legal guardians may utilize a COVID-19/MIS-C illness e-diary through an app (see Section 8.2.4) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms.

8.2.5. Pregnancy Testing

Pregnancy tests should be urine tests and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 2.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, or the participant's parent(s)/legal guardian, or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant/ participant's parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study

intervention), through and including 1 month after Dose 2 (Visit 4), from Dose 3 (Visit 5) through 1 month after Dose 3 (Visit 7), and from Dose 4 (Visit 8) through 1 month after Dose 4 (Visit 9). In addition, AEs occurring up to 48 hours after blood draws or collection of nasal swabs that are related to study procedures must be reported in the CRF.

SAEs will be collected from the time the participant provides informed consent through the duration of the study.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

Note: Symptoms that trigger potential COVID-19/MIS-C illness visits (Section 8.11) are expected endpoints and should not be recorded as AEs. These data will be captured only on the relevant illness pages of the CRF.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after Dose 3 of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant or participant's parent(s)/legal guardian with the Pregnant Partner Release of Information Form to deliver to the participant's partner. The investigator must document in the source documents that the participant or participant's parent(s)/legal guardian was given the Pregnant Partner Release of Information Form to provide to the participant's partner.

For a female participant who becomes pregnant, this information will be shared with the study participant's parent(s)/legal guardian if the participant's age is in accordance with local/country regulations.

8.3.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Symptoms that trigger potential COVID-19/MIS-C illness visits are expected endpoints (Section 8.11) and should not be recorded as AEs. These data will be captured only on the relevant illness pages of the CRF.

Potential COVID-19/MIS-C illness events and their sequelae will be reviewed by internal blinded case reviewers. Any SAE that is determined by the internal blinded case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that

the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

The following events are considered AESIs:

- A confirmed diagnosis of myocarditis or pericarditis. See Section 8.12 for additional procedures for monitoring of potential myocarditis or pericarditis.
- Exacerbation of underlying immunocompromising conditions. Please also refer to Section 10.2.1.

8.3.8.1. Lack of Efficacy

This section is not applicable, as efficacy is yet to be demonstrated in this study population.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE.**

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

Some of the blood samples collected for PBMC isolation and HLA typing may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires. The DNA and/or RNA samples from the blood sample for HLA typing may be used to further characterize HLA type.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.6.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.6.2. Specified Protein Research

Specified protein research is not included in this study.

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.9. Study Procedures

8.9.1. Visit 1 – Vaccination 1 (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent, and assent (where appropriate), will be obtained from the participant or participant's parent(s)/legal guardian. Each signature on the ICD and assent (where appropriate) must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD and assent (where appropriate). A copy of the signed and dated ICD and assent (where appropriate) must be given to the participant or participant's parent(s)/legal guardian. The source data must reflect that the informed consent and assent (where appropriate) was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- If a participant is eligible for the study, assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain the participant's significant medical history, including but not limited to conditions that put participants at high risk of developing severe outcomes of COVID-19 infection (see CDC listing at ***https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)***.

- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.

- Perform physical examination, evaluating 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.

- Measure vital signs (weight, height, oral temperature, pulse rate, and seated BP (for participants ≥5 years of age).

- Ensure that it is appropriate to and, if so, collect a blood sample for immunogenicity testing, dependent on participant age as referenced in Table 1 (Section 8), and to test for prior COVID-19. Please refer to the laboratory manual for further instructions.

- For participants who are eligible and have consented to PBMC sampling: ensure that it is appropriate to and, if so, collect a whole blood sample for PBMC isolation and HLA typing, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions.

- Obtain a nasal swab (collected by site staff) for determination of current SARS-CoV-2 status. Please refer to the laboratory manual for further instructions.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- If appropriate, discuss contraceptive use as described in Section 10.3.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Explain the e-diary technologies available for this study (see Section 8.2.4), and assist the participant or participant's parent(s)/legal guardian in downloading the study app onto the participant's or participant's parent(s)/legal guardian's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant or participant's parent(s)/legal guardian to complete the reactogenicity e-diary each day from Day 1 through Day 7, with Day 1 being the day of vaccination, and the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

- Record baseline systemic events in the e-diary.

- Obtain the participant's study intervention allocation using the IRT system.

- Staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IP manual for further instructions on this process.

- Staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 7 cm (>14 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Record AEs/SAEs as described in Section 8.3. AEs that occur prior to dosing should be noted on the medical history CRF.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

8.9.2. Visit 2 – Vaccination 2 (19 to 23 Days After Visit 1)

- Record AEs/SAEs as described in Section 8.3.

- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.

- Perform physical examination, evaluating 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.

- Measure vital signs (oral temperature, pulse rate, and seated BP (for participants ≥5 years of age). Height and weight do not need to be re-collected.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- If appropriate, discuss contraceptive use as described in Section 10.3.

- Obtain a nasal swab (collected by site staff) for determination of current SARS-CoV-2 status. Please refer to the laboratory manual for further instructions.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Ensure and document that the participant is still eligible to continue in the study. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, tolerability, and immunogenicity (see Section 7.1).

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- If potential COVID-19/MIS-C symptoms are present (Section 8.11), conduct a potential COVID-19/MIS-C illness visit, including a local laboratory SARS-CoV-2 test.

- Obtain the participant's study intervention allocation using the IRT system.

- Staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IP manual for further instructions on this process.

- Staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure that the participant or participant's parent(s)/legal guardian has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures, and if not, issue a measuring device and/or a thermometer (as required) and provide instructions on their use.

- Ensure that the participant or participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 7 cm (>14 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.
- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

8.9.3. Visit 3 – 1-Week Follow-Up Visit (After Vaccination 2) (6 to 8 Days After Visit 2)

Note: For participants who are not in the PBMC collection subset, this visit may be a telehealth visit.

- Record AEs/SAEs as described in Section 8.3.
- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.
- Ensure and document that the participant is still eligible to continue in the study.
- For participants who are eligible and have consented to PBMC sampling: ensure that it is appropriate to and, if so, collect a whole blood sample for PBMC isolation, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions.
- If appropriate, discuss contraceptive use as described in Section 10.3.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).
- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

- Schedule an appointment for the participant for the next study visit. Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.9.4. Visit 4 – 1-Month Follow-Up Visit (After Vaccination 2) (28 to 35 Days After Visit 2)

Note: Visit 4 and Visit 5 are expected to occur on the same day. All visit procedures should be conducted in consecutive order, and duplicative procedures listed in Visit 4 and Visit 5 need not be done.

- Record AEs/SAEs as described in Section 8.3.

- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.

- Ensure and document that the participant is still eligible to continue in the study.

- Ensure that it is appropriate to and, if so, collect a blood sample for immunogenicity testing, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions.

- If appropriate, discuss contraceptive use as described in Section 10.3.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).

- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

- Schedule an appointment for the participant for the next study visit. Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.9.5. Visit 5 – Vaccination 3 (28 to 35 Days After Visit 2)

- Record AEs/SAEs as described in Section 8.3.

- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.

- Measure vital signs (oral temperature, pulse rate, and seated BP (for participants ≥5 years of age). Height and weight do not need to be re-collected.

- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.

- Ensure and document that the participant is still eligible to continue in the study.

- If appropriate, discuss contraceptive use as described in Section 10.3.

- Obtain a nasal swab (collected by site staff) for determination of current SARS-CoV-2 status. Please refer to the laboratory manual for further instructions.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- If potential COVID-19/MIS-C symptoms are present (Section 8.11), conduct a potential COVID-19/MIS-C illness visit, including a local laboratory SARS-CoV-2 test.

- Obtain the participant's study intervention allocation using the IRT system.

- Staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IP manual for further instructions on this process.

- Staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure that the participant or participant's parent(s)/legal guardian has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures, and if not, issue a measuring device and/or a thermometer (as required) and provide instructions on their use.

- Ensure that the participant or participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant or participant's parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 7 cm (>14 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).

- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

- Schedule an appointment for the participant for the next study visit.

- Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity diary for collection at the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

8.9.6. Visit 6 – 1-Week Follow-Up Visit (After Vaccination 3) (6 to 8 Days After Visit 5)

Note: For participants not in the PBMC collection subset, this visit may be a telehealth visit.

- Record AEs/SAEs as described in Section 8.3.

- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.

- Ensure and document that the participant is still eligible to continue in the study.

- For participants who are eligible and have consented to PBMC sampling: ensure that it is appropriate to and, if so, collect a whole blood sample for PBMC isolation, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions.

- If appropriate, discuss contraceptive use as described in Section 10.3.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).

- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

- Schedule an appointment for the participant for the next study visit. Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.9.7. Visit 7 – 1-Month Follow-Up Visit (After Vaccination 3) (28 to 35 Days After Visit 5)

- Record AEs/SAEs as described in Section 8.3.
- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Ensure and document that the participant is still eligible to continue in the study.
- Ensure that it is appropriate to and, if so, collect a blood sample for immunogenicity testing, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions.
- If appropriate, discuss contraceptive use as described in Section 10.3.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).
- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.
- Schedule an appointment for the participant for the next study visit. Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.9.8. Visit 8 – Vaccination 4 (91 to 189 Days After Visit 5)

Note: The timing of Dose 4 should be determined by the investigator's discretion, taking into account factors such as the participant's underlying condition and level of immunosuppression, the evolving clinical literature, the COVID-19 incidence in the participant's geographic area, the potential for increased reactogenicity, and the risk of

reduced immunogenicity and antibody persistence with a shorter interval between Dose 3 and Dose 4.

- Record AEs/SAEs as described in Section 8.3.
- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.
- Ensure and document that the participant is still eligible to continue in the study.
- Measure vital signs (oral temperature, pulse rate, and seated BP) for participants ≥5 years of age. Height and weight do not need to be recollected.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- If appropriate, discuss contraceptive use as described in Section 10.3.
- Obtain a nasal swab (collected by site staff) for determination of current SARS-CoV-2 status. Please refer to the laboratory manual for further instructions.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- If potential COVID-19/MIS-C symptoms are present (Section 8.11), conduct a potential COVID-19/MIS-C illness visit, including a local laboratory SARS-CoV-2 test.
- Ensure that it is appropriate to and, if so, collect a blood sample for immunogenicity testing, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions. (Note: If the participant does not receive Dose 4 of BNT162b2, this blood draw is not required, and this visit may be conducted via telehealth).
- For participants who are eligible and have consented to PBMC sampling: ensure that it is appropriate to and, if so, collect a whole blood sample for PBMC isolation dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions.
- Obtain the participant's study intervention allocation using the IRT system.
- Staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IP manual for further instructions on this process.

- Staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form, as applicable.

- Ensure that the participant or participant's parent(s)/legal guardian has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures, and if not, issue a measuring device and/or a thermometer (as required) and provide instructions on their use.

- Ensure that the participant or participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant or participant's parent(s)/legal guardian to complete the reactogenicity e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 7 cm (>14 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.

- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).

- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.

- Schedule an appointment for the participant for the next study visit.

- Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity diary for collection at the next visit.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs

8.9.9. Visit 9 – 1-Month Follow-Up Visit (After Vaccination 4) (28 to 35 Days After Visit 8)

- Record AEs/SAEs as described in Section 8.3.
- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Ensure and document that the participant is still eligible to continue in the study.
- Ensure that it is appropriate to and, if so, collect a blood sample for immunogenicity testing, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions. (Note: If the participant does not receive Dose 4 of BNT162b2, this blood draw is not required, and this visit may be conducted via telehealth).
- If appropriate, discuss contraceptive use as described in Section 10.3.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant develops any symptoms as detailed in Section 8.11.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 8.12).
- The investigator or appropriately qualified designee reviews COVID-19/MIS-C illness e-diary data at frequent intervals.
- Schedule an appointment for the participant for the next study visit. Remind the participant or participant's parent(s)/legal guardian to bring the reactogenicity e-diary to the next visit.

- Complete the source documents. The investigator or an authorized designee completes the CRFs.

8.9.10. Visit 10 – 6-Month Follow-Up Visit (After Vaccination 4) (175 to 189 Days After Visit 8)

- Record AEs/SAEs as described in Section 8.3.
- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.
- Ensure and document that the participant is still eligible to continue in the study
- Ensure that it is appropriate to and, if so, collect a blood sample for immunogenicity testing, dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions
- For participants who are eligible and have consented to PBMC sampling: ensure that it is appropriate to and, if so, collect a whole blood sample for PBMC isolation dependent on participant age as referenced in Table 1 (Section 8). Please refer to the laboratory manual for further instructions. (Note: If the participant does not receive Dose 4 of BNT162b2, this blood draw is not required, and this visit may be conducted via telehealth).
- Collect the participant's e-diary or assist the participant or participant's parent(s)/legal guardian to remove the study app from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Inform the participant or participant's parent(s)/legal guardian that the participant's study participation has ended.

8.10. Unscheduled Visit for Fever or a Grade 3 or Suspected Grade 4 Reaction

If redness or swelling >14 units, Grade 3 pain (Section 8.2.4.2), a Grade 3 systemic event (Section 8.2.4.3), or fever (≥39.0°C [≥102.1°F]) (Section 8.2.4.4) is reported by the participant or participant's parent(s)/legal guardian in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.

If a suspected Grade 4 local reaction (Section 8.2.4.2), Grade 4 systemic event (Section 8.2.4.3), or fever (>40.0°C [>104.0°F]) (Section 8.2.4.4) is reported by the participant or participant's parent(s)/legal guardian in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm the fever and determine whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or participant's parent(s)/legal guardian recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.
- This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions/events should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.4.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.4.3.
- Assess for other findings associated with the reaction/event and record on the AE page of the CRF, if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.11. COVID-19 Surveillance (All Participants) and MIS-C Surveillance (Participants <21 Years of Age)

COVID-19 Surveillance: If a participant experiences any 1 of the following within a 24-hour period, from Visit 1 onwards (irrespective of perceived etiology or clinical significance), the participant or his/her parent(s)/legal guardian is instructed to contact the site immediately and, if in the opinion of the investigator a COVID-19/MIS-C illness visit is indicated, a potential COVID-19/MIS-C illness visit should be conducted. The test and visit would be optimal within 3 days after symptom onset (and at the latest 4 days after symptom resolution). During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that he or she is SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed. If the result is positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

MIS-C Surveillance: If a participant experiences a hospitalization for a severe illness with no other alternative etiology, the participant's parent(s)/legal guardian is instructed to contact the site immediately and participate in an in-person or telehealth visit as soon as possible, optimally within 3 days after symptom onset (and at the latest 4 days after symptom resolution). Note that if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness, and a second illness visit is not required.

COVID-19/MIS-C Surveillance

The participant or participant's parent(s)/legal guardian may utilize a COVID-19/MIS-C illness e-diary through an app (see Section 8.2.4) installed on a provisioned device or on a personal device to report any symptoms listed below. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

In addition, the following symptoms are for participants who are ≤12 years of age:

- Hospitalization for a severe illness with no other alternative etiology;
- Hospitalization due to confirmed COVID-19 infection;
- Inability to eat/poor feeding in participants <5 years of age;
- Abdominal pain.

Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness, and a second illness visit is not required.
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

8.11.1. Potential COVID-19/MIS-C Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, thus allowing the participant or participant's parent(s)/legal guardian and investigator to communicate on aspects of clinical care.

As a participant's COVID-19/MIS-C illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs/SAEs as described in Section 8.3. Symptoms that trigger potential COVID-19/MIS-C illness visits (Section 8.11) are expected endpoints and should not be recorded as AEs. These data will be captured only on the relevant illness pages of the CRF.

- Record details of medications currently taken and nonstudy vaccinations as described in Section 6.8.

- If the visit is conducted in person, obtain a nasal swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal swab or request the participant's parent(s)/legal guardian to collect a nasal swab from the participant and ship for assessment as instructed. Note: Participants in Mexico will not self-collect nasal swabs.

- Collect COVID-19/MIS-C–related standard-of-care clinical and laboratory information. This includes symptoms and signs including, but not limited to:

  - Clinical signs at rest indicative of severe systemic illness:

    - RR (breaths/min) and HR (beats/min) as shown in Table 2[21] (Section 8.1.1);

    - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg)[22];

    - 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 ULN for age or 2-fold increase in baseline creatinine);

  - Significant GI/hepatic failure (TBili ≥4 mg/dL or ALT 2 times ULN for age); or

  - Significant neurological dysfunction: Glasgow Coma Scale score ≤11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline[22];

- Admission to an ICU;
- Collect MIS-C data:
  - Additional clinical signs and symptoms related to hematologic, dermatologic, and/or other;
  - Any potential cardiac, respiratory, neurological, or GI/hepatic complications;
  - COVID-19 exposure within the 4 weeks prior to the onset of symptoms;
  - Imaging (chest, abdominal, etc), CSF studies, and/or echocardiogram;
- Clinical diagnosis;
- Local laboratory SARS-CoV-2 test result(s), including RT-PCR, serology, or antigen test. Note that, if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal swab should also be obtained and shipped for assessment at the central laboratory;
- Full blood count, blood chemistry, specifically creatinine, urea, LFTs, and CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6 if available;
- Number and type of any healthcare contact; duration of hospitalization and ICU stay;
- Death.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.12. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

8.13. Communication and the Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study app, a communication pathway between the participant or participant's parent(s)/legal guardian and the study site staff will be established. The participant or participant's parent(s)/legal guardian may be able to utilize his/her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant to report whether or not the participant has experienced symptoms that could represent a potential COVID-19/MIS-C illness (see in Section 8.11).
- A platform for recording local reactions and systemic events (reactogenicity e-diary) (see Section 8.2.4).

If a participant or participant's parent(s)/legal guardian is not actively completing either the reactogenicity or COVID-19/MIS-C illness e-diary, the investigator or designee is required to contact the participant or participant's parent(s)/legal guardian to ascertain why and also to obtain details of any missed events.

8.14. SARS-CoV-2 NAAT Results From Visit 1 and Subsequent Vaccination Visits and Potential COVID-19 Illness Visits

Nasal swabs for SARS-CoV-2 NAAT are obtained at:

- Visit 1 and subsequent vaccination visits: to determine whether a participant has serological or virological evidence of past SARS-CoV-2 infection.
- Potential COVID-19/MIS-C illness visits: to determine whether symptoms experienced by the participant fulfill the COVID-19/MIS-C case definition.

Research laboratory–generated positive results from the swabs taken at or after Visit 1, and all results from the potential COVID-19 illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant or participant's parent(s)/legal guardian should be directed to seek additional testing through the participant's primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result after Visit 1 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at or after Visit 1 or any time between Visit 1 and subsequent vaccination visits: Subsequent vaccinations should proceed as normal.

- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): Subsequent vaccination may be given if all other eligibility criteria are met and no temporary delay criteria are met, and the participant should remain in the study.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a SAP, which will be maintained by the sponsor. 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.

9.1. Statistical Hypotheses

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

9.1.1. Estimands

The estimands corresponding to each primary and exploratory objective are described in the table in Section 3.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population (Section 9.2). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

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

9.1.2. Multiplicity Adjustment

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

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	All participants who have a signed ICD and assent (where appropriate).
Assigned to study intervention	All participants who are assigned an enrollment number in the IRT system.
Dose 3 evaluable immunogenicity	All eligible participants who receive 3 doses of the vaccine with Dose 2 and Dose 3 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window after Dose 3, and have no other important protocol deviations as determined by the clinician.
Dose 4 evaluable immunogenicity	All eligible participants who receive 3 doses of the vaccine with Dose 2, Dose 3, and Dose 4 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window after Dose 4, and 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.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and exploratory endpoints.

9.3.1. General Considerations

All safety and immunogenicity data will be summarized 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 specified otherwise.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population. An additional analysis will be performed based on the all-available immunogenicity population if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population.

The safety analyses will be based on the safety population.

9.3.1.1. Analysis 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% CIs for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).

9.3.1.2. Analysis for Continuous Data

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

9.3.1.2.1. 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.

9.3.1.2.2. 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.

9.3.1.2.3. Reverse Cumulative Distribution Curve

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.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMT of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 and 1 month after Dose 4 in participants without serological or virological evidence of past SARS-CoV-2 infection** The GMT of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 and 1 month after Dose 4, and the associated 2-sided 95% CI, will be provided for participants without serological or virological evidence of past SARS-CoV-2 infection. Statistical methods are described in Section 9.3.1.2.1.
Safety	Descriptive statistics will be provided for each reactogenicity endpoint for each dose. Local reactions and systemic events from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination) will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs (see Section 9.3.1.1). AEs and SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of 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, and SAEs from Dose 1 through the duration of the study will be provided.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Not applicable.

9.3.4. Exploratory Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Immunogenicity	**GMTs of SARS-CoV-2 neutralizing titers in participants without serological or virological evidence of past SARS-CoV-2 infection** GMTs and the associated 2-sided 95% CIs will be provided for participants with no serological or virological evidence of past SARS-CoV-2 infection using the same statistical analysis method described above for the primary endpoints at the following time points: 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. Participants' data will be excluded from the time point that the participant has a positive or missing NAAT or N-binding result. **GMFRs of SARS-CoV-2 neutralizing titers in participants without serological or virological evidence of past SARS-CoV-2 infection** GMFRs from before vaccination to 1 month after Dose 2, from before vaccination to 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4, and the associated 2-sided 95% CIs, will be provided for participants with no serological or virological evidence of past SARS-CoV-2 infection. Participants' data will be excluded from the time point that the participant has a positive or missing NAAT or N-binding result. GMFRs will be limited to participants with nonmissing values prior to the vaccination and at the postvaccination time point. The statistical methods are described in Section 9.3.1.2.2. **Percentages of participants with seroresponse in participants without serological or virological evidence of past SARS-CoV-2 infection** The percentages of participants with seroresponse and the associated 2-sided 95% Clopper-Pearson CIs will be provided at 1 month after Dose 2, 1 month after Dose 3, and 1 month and 6 months after Dose 4. Seroresponse is defined as achieving ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. In addition, GMTs, GMFRs, and percentages of participants with seroresponse at each time point, along with the associated 95% CI,

Endpoint	Statistical Analysis Methods
	will be provided for participants with and without evidence of past SARS-CoV-2 infection using same methods described above. Subgroup analyses of immunogenicity endpoints based on various time points for Dose 3 administration may be performed.
Incidence and genotypic lineage of confirmed COVID-19	Counts, incidence of confirmed COVID-19 cases per 1000 person-years of follow-up, and the associated 2-sided 95% CIs will be provided. Summary of genotypic lineage of SARS-CoV-2 will be provided for confirmed COVID-19 cases.
MIS-C incidence	Counts, incidence of confirmed MIS-C cases per 1000 person-years of follow-up, and the associated 2-sided 95% CIs will be provided.

9.4. Interim Analyses

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

9.4.1. Analysis Timing

Statistical analyses may be carried out when the final data for 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.

9.5. Sample Size Determination

The study size is not based on any formal hypothesis test. All statistical analyses will be descriptive.

Table 7 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes based on anticipated enrollment in each subgroup. For example, if the true AE rate is 1%, with 60 participants in a group, there is 45% probability of observing at least 1 AE.

Table 7. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Sample Size (N)	Assumed True Event Rate of an AE						
	0.5%	1%	2%	3%	5%	7%	10%
10	0.05	0.09	0.18	0.26	0.40	0.52	0.65
60	0.26	0.45	0.70	0.84	0.95	0.99	>0.99

Note: A total of 60 participants are to be vaccinated within each disease subset of participants ≥18 years of age; at least 10 participants are to be vaccinated within each disease subset in each younger age group.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD(s), assent(s), SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and where appropriate his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and where appropriate his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own assent, the source documents must record why the participant did not provide assent (for example, minor child), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority during the study, as recognized under local law, they must be reconsented as adults to remain in the study. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, they must provide documentation of legal status to give consent without the permission of the participant's parent(s)/legal guardian.

Participants and where appropriate their parent(s)/legal guardian must be informed that their participation is voluntary. Participants or where appropriate their parent(s)/legal guardians will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant, and where appropriate the participant's parent(s)/legal guardian, is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

Participants and where appropriate the participants' parent(s)/legal guardians must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participants and where appropriate their parent(s)/legal guardians.

The participants and where appropriate participants' parent(s)/legal guardians must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant, and where appropriate the participant's parent(s)/legal guardian, is fully informed about the participant's right to access and correct the participant's personal data and to withdraw consent for the processing of the participant's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardians in certain regions.

The source documentation must include a statement that written informed consent, and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants, and where appropriate parent(s)/legal guardians, must be reconsented to the most current version of the ICD(s)/assent during the participant's participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

If participants are rescreened, the participants or where appropriate the participants' parent(s)/legal guardians are required to sign a new ICD/assent (as applicable).

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for

determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Committees Structure

10.1.5.1. 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 will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the EU Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs and assents (where appropriate), pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory retain notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Study Monitoring Plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study ID number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occunence in a patient or clinical study paiiicipant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abno1mal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abno1mal laborato1y test results (hematology, clinical chemistiy, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnonnal laborato1y test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medicaVsurgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustinents) or discontinuation from the study, significant additional conc01nitant drng ti·eatinent, or other therapy.
 	
• Exacerbation of a chronic or inte1mittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administi·ation, even though it may have been present before the staii of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drng-drng interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible

suicidal/self-hanning intent. Such overdoses should be reported regardless of sequelae.

Events	Meeting the AE Definition
	• Any clinically significant abno1mal laborato1y findings or other abno1mal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the paiiicipant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untowai·d medical occunence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the staii of the study that do not worsen.

10.2.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The tenn "life-threatening" in the definition of "serious" refers to an event in which the paiiicipant was at risk of death at the time of the event. It does not refer to an event that hypothetically inight have caused death if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency wai·d for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding.	All AEs or SAEs associated with exposure during pregnancy or breastfeeding. **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE).* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laborato1y repo1is, and diagnostic repo1is) related to the event.
- The investigator will then record all relevant AE or SAE info1mation in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the paiiicipant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Repo1iing Fonn/AE or SAE CRF page.
- There may be instances when copies of medical records for ce1iain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the paiiicipant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical info1mation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ied during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For pmposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with paiiicipant's usual function.
2	MODERATE	Interferes to some extent with paiiicipant's usual function.
3	SEVERE	Interferes significantly with paiiicipant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occmTence of each AE or SAE. The investigator will use clinical judgment to detennine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or argmnents to suggest a causal relationship, rather than a relationship cannot be rnled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administrntion, will be considered and investigated.
- The investigator will also consult the IB and/or product infonnation, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **!!!!!.U** docUillent in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occmTed, and the investigator has minimal info1mation to include in the initial repo1i to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up info1mation and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when dete1mining regulato1y repo1iing requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for repo1iing pmposes, as defined by the sponsor. In addition, if the investigator dete1mines that an SAE is associated with study procedmes, the investigator must record this causal relationship in the somce docUillents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Repo1iing Fonn and in accordance with the SAE repo1iing requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perfonn or aiTange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laborato1y tests or investigations, histopathological exaininations, or consultation with other healthcare providers. • If a paiiicipant dies during paiiicipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1iem findings, including histopathology. • New or updated infonnation will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the infonnation.

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primaiy mechanism for reporting a SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to repo1i the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entiy of new data or changes to existing data. • If a site receives a report of a new SAE from a study paiiicipant or receives updates data on a previously repo1ied SAE after the electi·onic data collection tool has been taken offline, then the site can repo1i this infonnation on paper SAE fo1m (see next section (or to Pfizer Safety by telephone).

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Repo1iing Fonn is the prefe1Ted method to transmit this info1mation to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Repo1iing Fo1m sent by overnight mail or con ne r serv ce.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Repo1iing Fonn pages within the designated repo1iing time frames.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
    - In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.3.4).

10.3.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.3.3).
- OR
- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.3.3. Woman of Childbearing Potential

A female participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Female participants in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.4. Contraception Methods

Contraceptive use by male or female participants should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

    - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.5. Appendix 5: Genetics

Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention, as well as susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA and/or RNA analysis.

- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.5) will be stored for up to 15 years or other period as per local requirements.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Alternative Measures During Public Emergencies

10.6.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Every effort should be made to bring the study participant to their scheduled visit. If the participant or participant's parent(s)/legal guardian is unable to, as a minimum, the following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 3 regarding pregnancy tests.

Study participants or their parent(s)/legal guardians must be reminded to promptly notify site staff about any change in the participant's health status.

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 4 (21 January 2022)

Overall Rationale for the Amendment: Updating procedures to allow a fourth dose (booster), reducing the window for provision of Dose 3, and allowing vaccination with the age-appropriate dose

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Section 1.3 – Schedule of Activities, Section 4.1 – Overall Design, Section 4.3 – Justification for Dose, and Section 6: Study Intervention(s) and Concomitant Therapy Section 8.9 – Study Procedures	• Added a fourth dose (booster), and 1 and 6 months post-Dose 3 visits, with associated objectives • Reduced the Visit 5 window for provision of Dose 3 • Clarified that if Visit 4 and Visit 5 occur on the same day, duplicate procedures need not be conducted • Updated procedures to allow vaccination with the age-appropriate dose	• In line with regulatory recommendations for providing third/fourth doses of BNT162b2 to immunocompromised individuals
Section 1.3 – Schedule of Activities	• Removed immunogenicity blood collection at Visit 5 and Visit 6 • Removed PBMC collection at Visit 5 and Visit 7 • Updated Visit 6 to allow conducting via telephone for participants not in the PBMC subset	• To streamline the schedule of visits and blood draws, taking into account the fixed timing of Dose 3 and the addition of a fourth dose (booster)
Section 9.2 – Analysis Sets Section 9.3 – Statistical Analyses	• Clarified the definition of Dose 3 and Dose 4 evaluable immunogenicity analysis sets	• In line with regulatory recommendations for providing third/fourth doses of BNT162b2 to

Section # and Name	Description of Change	Brief Rationale
Section 9.4 – Interim Analyses	• Updated wording to align with the modified objectives and endpoints • Removed the analysis timing at 1 month after Dose 2 and added the 1 month after Dose 4 analysis	immunocompromised individuals
Section 10.2.4 – Reporting of SAEs	• Added a mechanism for reporting SAEs electronically	• To allow multiple routes to report SAEs

Amendment 3 (15 September 2021)

Overall Rationale for the Amendment: To remain in alignment with changing regulatory guidance on administering Dose 3

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis, Section 1.3 – Schedule of Activities, Section 4.1 – Overall Design, Section 4.3 – Justification for Dose, and Section 8.9 – Study Procedures	• Updated the Visit 5 window to allow its occurrence as early as 28 days after Visit 2 • Clarified that if Visit 4 and Visit 5 occur on the same day, duplicate procedures need not be conducted; Visit 5 immunogenicity blood draws are not required in this circumstance	• In line with regulatory recommendations for providing a third dose of BNT162b2 to immunocompromised individuals
Section 9.3.4 – Exploratory Endpoint(s)/Estimand(s) Analysis	• Updated wording to allow subgroup analysis of immunogenicity endpoints based on various time points for Dose 3 administration	• This analysis may be performed in line with regulatory recommendations for providing a third dose of BNT162b2 to immunocompromised individuals, as the vaccination window may vary

Amendment 2 (05 August 2021)

Overall Rationale for the Amendment: As individuals with compromised immune systems are at significant risk of morbidity and mortality due to SARS-CoV-2 infection, it is imperative that the safety, tolerability, and immune response to vaccination among these individuals be investigated. Therefore, the conditions for study participants ≥18 years of age include NSCLC, CLL, hemodialysis treatment secondary to end-stage renal disease, and participants ≥2 to <18 years of age with representative conditions, including those with inflammatory and autoimmune inflammatory disorders receiving immunomodulators, those who have undergone organ transplant and are receiving maintenance antirejection modulators, and those who have undergone bone marrow or stem cell transplant.

The changes in this amendment include the removal of the upper age limit for the cohort of participants on active immunomodulator therapy (eg, TNFα inhibitors, tofacitinib, or MTX) for an autoimmune inflammatory disorder (eg, inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, and inflammatory bowel disease, such as ulcerative colitis and Crohn's disease) and the addition of risks associated with myocarditis and pericarditis as well as their subsequent unplanned visits, as committed to CBER.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 – Risk Assessment	• Updated the risk assessment for participants in this study	• Risk assessment has been further informed, including the very rare cases of myocarditis, pericarditis, and anaphylaxis reported after authorization in recipients of BNT162b2
Section 3 – Objectives, Endpoints, and Estimands	• Added primary and exploratory safety, tolerability, and immune response objectives for the expanded cohort of participants on active immunomodulator therapy	• This update has been implemented to allow the expanded cohort to follow the same primary and exploratory objectives as the other cohorts in the study

Section # and Name	Description of Change	Brief Rationale
Section 4.1 – Overall Design	• Clarified wording on participants in the cohort who are taking active immunomodulator therapy	• This update clearly documents the intended therapies for participants who are part of this cohort
Section 5 – Study Population	• Clarified wording on diversity of recruitment	• This addition will enable collection of race and ethnicity data in prescreeners
Section 5.1 – Inclusion Criteria	• Clarified wording on inclusion criterion 4 to specify that the participant or participant's parent(s)/legal guardians, as age appropriate, need to be able to be contacted by telephone throughout the study	• This update clearly documents the intended criterion for participants to meet in order to be enrolled into this study
Section 6.8.1 – Prohibited During the Study	• Included explanatory text on the removal of prohibition on concomitant vaccinations within 28 days before and after vaccination with BNT162b2	• This update has been implemented in line with CDC guidelines as of June 2021
Section 6.8.2 – Permitted During the Study	• Inserted text to allow flexibility of immunomodulator administration before and after vaccination with BNT162b2	• This update has been implemented to clarify that the alteration of immunomodulator administration is permitted according to local guidelines
Section 8 – Study Assessments and Procedures	• Expanded the subset of participants participating in PBMC collection	• This update has been implemented to allow the expanded cohort to follow similar procedures to other participants who have consented to PBMC collection

Section # and Name	Description of Change	Brief Rationale
Section 8.3.8 – Adverse Events of Special Interest	• Added myocarditis and pericarditis	• This update has been implemented in response to commitments made to CBER
Section 8.9 – Study Procedures	• Added a visit procedure to any visit that occurs sooner than 1 month after any vaccination requesting that participants or participant's parent(s)/legal guardian to contact site staff or the investigator if the participant experiences acute chest pain, shortness of breath, or palpitations	• This update has been implemented in response to commitments made to CBER
Section 8.12 – Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis	• Added an unplanned visit to capture data pertaining to myocarditis and pericarditis	• This visit has been implemented in response to commitments made to CBER
Section 9.4.1 – Analysis Timing	• Updated wording to reflect the addition of the new cohort of participants ≥18 years of age receiving treatment for an autoimmune inflammatory disorder	• This update clearly reflects the new number of cohorts in the study
Section 10.7 – Appendix 7: Protocol Amendment History	• Added Appendix 7 to include the protocol amendment history and moved the Protocol Amendment Summary of Changes Table for Protocol Amendment 1 from the beginning of the document to this new section	• This update ensures only the latest Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents

Amendment 1 (24 June 2021)

Overall Rationale for the Amendment: Addition of dose levels for participants ≥5 to <12 and <5 years of age

Section # and Name	Description of Change	Brief Rationale
Section 2.3 – Benefit/Risk Assessment	• Added safety text indicating that no specific safety concerns were identified by subgroup analysis by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection	• Benefit/risk assessment has been further informed by the C4591001 study data
Section 3 – Objectives, Endpoints, and Estimands	• Removed the exploratory objective to describe viral shedding in line with the removal of the convalescent visit	• As the convalescent visit will no longer be conducted, the swabs intended for this exploratory analysis will no longer be collected
Section 5.2 – Exclusion Criteria	• Added the exclusion criterion for participants with insufficient deltoid muscle mass	• This exclusion criterion was added to ensure participant safety, so that those with insufficient muscle mass are not vaccinated
Section 5.5 – Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention	• Clarified that symptoms indicative of COVID-19 illness, in the opinion of the investigator, meet the criteria for temporarily delaying vaccine administration	• This clarification was added in line with other C459 program studies
Section 6 – Study Intervention(s) and Concomitant Therapy	• Clarified that study age groups are assigned by age at Visit 1; participants will receive the same dose level at all 3 vaccination visits	• This clarification was added in response to Investigator questions
Section 6.1 – Study Intervention(s) Administered	• Added the 10-µg dose level for participants ≥5 to <12 years of age	• This dose level was determined by data from the C4591007 study

Section # and Name	Description of Change	Brief Rationale
Section 6.1 – Study Intervention(s) Administered	• Added the 3-µg dose level for participants <5 years of age	• This dose level was determined by data from the C4591007 study
Section 8.9 – Study Procedures	• Clarified visit procedures for participants in the PBMC subset	• Clarification was added that the PBMC blood draw (and inclusion in the PBMC subset) is only for those participants who are eligible and have consented to this procedure
Section 8.9.3 – Visit 3 – 1-Week Follow-up Visit (After Vaccination 2) (6 to 8 Days After Visit 2)	• Added wording to allow Visit 3 to be conducted via telehealth for participants not in the PBMC subset	• As in-person procedures are not required for these participants at Visit 3, this visit may be conducted via telehealth
Section 8.11.1 – Potential COVID-19/MIS-C Convalescent Visit (28 to 35 Days After Potential COVID-19 Illness Visit)	• Removed the requirement to conduct a potential COVID-19/MIS-C convalescent visit following each COVID-19/MIS-C illness visit	• Sufficient data were collected in Study C4591001
Section 9.2 – Analysis Sets	• Clarified that participants are not randomized	• As this is an open-label study and study intervention will be assigned to participants, no randomization will occur
Section 9.4 – Interim Analyses	• Clarified that, as this is an open-label study, the sponsor may conduct reviews of all available safety and immunogenicity data during the course of the study	• This update clearly documents the intended data reviews during the study
Section 9.4 – Interim Analyses	• Clarified that no formal interim analysis will be conducted for this study, but analyses may be	• This update clearly documents the intended

Section # and Name	Description of Change	Brief Rationale
	carried out when the final data for specified objectives for a particular cohort (out of the 6 cohorts; participants ≥18 years of age receiving treatment for CLL, NSCLC, and end-stage renal disease; participants ≥2 to <5, ≥5 to <12, and ≥12 to <18 years of age) are available	data analyses during the study
Section 9.4.1 – Analysis Timing	• Removed the analysis at 7 days after Dose 3	• Analysis is being conducted 1 month after Dose 3, which is a more appropriate timepoint to look at responses following vaccination in an immunosuppressed population

10.8. Appendix 8: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
app	application
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransferase
BCL-2	B-cell lymphoma-2
BCR	B-cell receptor
BiPaP	bilevel positive airway pressure
BNP	brain natriuretic peptide
BP	blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BTK	Bruton tyrosine kinase
CBER	Center for Biologics Evaluation and Research
CD20	B-lymphocyte antigen CD20
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLL	chronic lymphocytic leukemia
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSR	clinical study report
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee

Abbreviation	Term
ECC	emergency contact card
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GMFR	geometric mean fold rise
GMT	geometric mean titer
GVHD	graft-vs-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IgG	immunoglobulin G
IL-6	interleukin 6
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual

Abbreviation	Term
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
IV	intravenous(ly)
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MET	hepatocyte growth factor receptor
MHRA	Medicines and Healthcare Products Regulatory Agency
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
MTX	methotrexate
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NTRK	neurotrophic tyrosine kinase (gene)
PACL	protocol administrative change letter
PaO_2	partial pressure of oxygen, arterial
PASS	postauthorization safety study
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PI	principal investigator
PI3K	phosphoinositide 3-kinase
PPE	personal protective equipment
PT	prothrombin time
PTLD	posttransplant lymphoproliferative disorder
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RET	rearranged during transfection
RMP	risk management plan
RNA	ribonucleic acid
ROS1	[gene encoding] proto-oncogene tyrosine-protein kinase
RR	respiratory rate

Abbreviation	Term
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
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
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCR	T-cell receptor
Th1	T-helper type 1
TNFα	tumor necrosis factor alpha
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vax	vaccination
VE	vaccine efficacy
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

11. REFERENCES

1 World Health Organization. Timeline: WHO's COVID-19 response. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#!. Accessed: 08 Jan 2021.

2 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published: 11 Mar 2020. Accessed: 01 Apr 2020.

3 Pfizer and BioNTech. Vaccines and Related Biological Products Advisory Committee Meeting, December 10, 2020. FDA briefing document: Pfizer-BioNTech COVID-19 vaccine. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; Dec 2020.

4 Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med. 2020;383(25):2439-50.

5 Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383(4):334-46.

6 Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med. 2020;383(4):347-58. DOI: 10.1056/NEJMoa2021756.

7 Ma L, Zhang YY, Yu HG. Clinical manifestations of Kawasaki disease shock syndrome. Clin Pediatr (Phila). 2018;57(4):428-35.

8 Li Y, Zheng Q, Zou L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. Pediatr Rheumatol Online J. 2019;17(1):1.

9 Levin M. Childhood multisystem inflammatory syndrome - a new challenge in the pandemic [editorial]. N Engl J Med. 2020;383(4):393-5. DOI: 10.1056/NEJMe2023158.

10 Godfred-Cato S, Bryant B, Leung J, et al. COVID-19–associated multisystem inflammatory syndrome in children—United States, March–July 2020 [published erratum appears in MMWR Morb Mortal Wkly Rep. 2020;69(35):1229]. MMWR Morb Mortal Wkly Rep. 2020;69(32):1074-80.

11 Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20(11):e276-e288.

[12] Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771-8.

[13] Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.

[14] Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated: 02 Nov 2020. Accessed: 17 Nov 2020.

[15] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-15.

[16] Sahin U, Muik A, Vogler I, et al. BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. MedRxiv. 2020. DOI: https://doi.org/10.1101/2020.12.09.20245175.

[17] US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

[18] U.S. Census Bureau. QuickFacts: United States. Available from: https://www.census.gov/quickfacts/fact/table/US/PST045219. Accessed: 14 Apr 2021.

[19] US Food and Drug Administration. Guidance for industry: development and licensure of vaccines to prevent COVID-19. Rockville, MD: Centers for Biologics Evaluation and Research; June 2020.

[20] Centers for Disease Control and Prevention. COVID-19: people with certain medical conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Updated: 29 Dec 2020. Accessed: 25 Jan 2021.

[21] 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.

[22] Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8. DOI: 10.1097/01.PCC.0000149131.72248.E6.

[23] Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Available from: https://www.cdc.gov/mis-c/hcp/. Accessed: 09 Dec 2020.

Document Approval Record

Document Name:	C4591024 Protocol Amendment 5 Clean Copy, 13 Jan 2023
Document Title:	A PHASE 2b, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF VACCINE CANDIDATE BNT162b2 IN IMMUNOCOMPROMISED PARTICIPANTS ≥2 YEARS OF AGE

Signed By:	Date(GMT)	Signing Capacity
PPD	13-Jan-2023 15:18:58	Final Approval
PPD	13-Jan-2023 16:56:02	Final Approval
PPD	16-Jan-2023 14:16:24	EUQPPV Approval