



**A PHASE 1, OPEN-LABEL DOSE-FINDING STUDY TO EVALUATE SAFETY,
TOLERABILITY, AND IMMUNOGENICITY AND PHASE 2/3
PLACEBO-CONTROLLED, OBSERVER-BLINDED SAFETY, TOLERABILITY,
AND IMMUNOGENICITY STUDY OF A SARS-COV-2 RNA VACCINE
CANDIDATE AGAINST COVID-19 IN HEALTHY CHILDREN**

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Study Conducted By	Pfizer
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Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children

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Protocol Amendment Summary of Changes Table

Document History		
Document	Version Date	Summary and Rationale for Changes
Amendment 8	28 Apr 2023	<ul style="list-style-type: none"> Added language to permit early completion of this clinical trial as agreed with the FDA and EMA. <ul style="list-style-type: none"> Updated schedules of assessments and protocol text to identify study visits that no longer need to be completed. Updated study procedures to describe site actions following approval of protocol amendment 8. Removed the lower-dose-evaluation substudy of the protocol. The FDA has approved the request for the lower-dose evaluation postmarketing commitment release in November 2022. <ul style="list-style-type: none"> Removed corresponding sections and wording throughout the protocol text. Incorporated PACLs for the period of April to October 2022. <ul style="list-style-type: none"> Provided further guidance for participants withdrawal from the study for Phase 2/3 selected-dose parents/legal guardians that decline the blinded third dose. Added a statement that participants in Mexico will not self-collect nasal swabs per Mexican regulatory request. Clarified that the Release of Maternal COVID-19 Vaccination Information Form is required to be signed by the biological mother of the child enrolled in the ≥ 6-month to < 2-year age group prior to the collection of information on any COVID-19 vaccination received during pregnancy. Clarified that the window for provision of a third dose of BNT162b2 for participants ≥ 5 years of age to < 12 years of age in the US is in line with changing regulatory requirements (emergency use approvals). Added the instruction that once an applicable local or national recommendation for the COVID-19 vaccination has been made in any participating country, it is intended that unblinding and vaccination of placebo recipients with BNT162b2 is to occur for all study participants, regardless of location. Removed blood sample collection for immunogenicity testing at certain study visits for Phase 1 dose-finding participants and Phase 2/3 selected-dose participants who are part of the immunogenicity subset to reduce the burden of procedures on participants and caregivers for those enrolling in study C4591048. Secondary/exploratory objectives with corresponding text throughout the protocol removed: <ul style="list-style-type: none"> To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants ≥ 5 to < 12 years age in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection.

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Document History		
Document	Version Date	Summary and Rationale for Changes
		<ul style="list-style-type: none"> ○ To describe the immune responses elicited by prophylactic BNT162b2 at the selected dose level at varying intervals between Dose 2 and Dose 3 in the selected-dose portion of the study. ○ To describe the serological responses in Phase 2/3 participants in the selected-dose portion of the study to BNT162b2 at the dose level selected in each age group in cases of: <ul style="list-style-type: none"> • Confirmed COVID-19 with and without coinfection • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19 • Added exploratory objective to describe the incidence of confirmed COVID-19 through the entire study follow-up period. <ul style="list-style-type: none"> ○ Added corresponding estimands, endpoints, and statistical analysis methods.
Amendment 7	10 Mar 2022	<ul style="list-style-type: none"> • Given the emerging data in individuals 16 years of age and older, an additional (third) dose of BNT162b2 at least 5 months after Dose 2 to all Phase 2/3 participants enrolled to support obtaining serum samples for potential troponin I testing (≥ 5 to <12 years of age, placebo-controlled, and ≥ 12 to <16 years of age, open-label): <ul style="list-style-type: none"> • Revised corresponding objectives, estimands, and endpoints • Revised corresponding SoA and procedures • Added details in the statistical methods sections. • Clarified both symptomatic and asymptomatic COVID-19 infection will result in temporary delay of enrollment, randomization, or study intervention administration. • Clarified that the dose interval for Phase 2/3 selected-dose participants enrolled in the ≥ 2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will be the same as for the ≥ 5 to <12 years age group (ie, third dose administered at least 6 months after the second dose). • Additional clarification for Phase 2/3 selected-dose parents/legal guardians that decline the blinded third dose. • Added flexibility to inclusion and exclusion criteria (based on investigator's judgment) for Phase 1 dose-finding participants when receiving Dose 3. • Clarified that, for Phase 1 dose-finding participants, height and weight should be collected once at Visit 1 only as part of the physical examination; likewise, the participant's randomization number and study intervention allocation are obtained using the IRT system at Visit 1 only.

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Document	Version Date	Summary and Rationale for Changes
		<ul style="list-style-type: none"> Added a relative VE objective for 3-dose BNT162b2 from original active vaccine group vs 2-dose BNT162b2 from placebo crossover. The relative VE calculation for those receiving 3 doses of BNT162b2 is being compared to those who received 2 doses of BNT162b2 after originally receiving placebo (as opposed to comparing to those who received 2 doses of BNT162b2, as originally randomized) due to the emergence of different variants over time; the timing of cases for these 2 groups are similar, therefore making it more likely to compare cases of the same variant. Added collection of maternal COVID-19 immunization and breastfeeding data for participants who are ≥ 6 months to < 2 years of age in the Phase 2/3 selected-dose portion of the study. Updated the risk assessment to align with the current version of the IB.
Amendment 6	04 Jan 2022	<ul style="list-style-type: none"> The primary immunogenicity analysis demonstrated that the immune response elicited by BNT162b2 in participants ≥ 2 to < 5 years of age (2 doses at 3 μg) did not meet immunobridging criteria when compared to participants 16 to 25 years of age from the C4591001 study. As a result, and given the emerging data in individuals 16 years of age and older, an additional (third) dose of BNT162b2 will be administered to all Phase 1 dose-finding and Phase 2/3 selected-dose participants: <ul style="list-style-type: none"> Added corresponding objectives, estimands, and endpoints Added corresponding SoA and procedures Added details in the statistical methods sections. Cell-mediated immune responses will also be described following isolations of PBMCs in a subset of Phase 2/3 participants who receive a third dose. An additional 4500 Phase 2/3 selected-dose participants ≥ 6 months to < 2 years and ≥ 2 to < 5 years of age are permitted to enroll to enlarge the size of the pediatric safety database. Clarified that participants who decline the opportunity to receive a third dose should be withdrawn. Clarified that the interval between the second and third doses will be based on the participant's age at the time of enrollment. Clarified that the dose level of BNT162b2 will be based on age at the time of vaccination. As the asymptomatic efficacy objective is now restricted to participants ≥ 5 to < 12 years of age, in the Phase 2/3 selected-dose portion, participants ≥ 6 months to < 5 years of age who enrolled before protocol amendment 6 will no longer have a blood sample for immunogenicity testing at Visit 5 (6-month follow-up). Time frames for prohibited nonstudy vaccines were simplified. For the option of a 3-μg dose level, an additional unit dose strength was added.

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Document	Version Date	Summary and Rationale for Changes
		<ul style="list-style-type: none"> For participants <5 years of age, all positive RT-PCR cases confirmed by the central laboratory will undergo BioFire testing.
Amendment 5	15 Nov 2021	<ul style="list-style-type: none"> Based on the 10-µg immunobridging data in the ≥5- to <12-year age group, revised Phase 1/2/3 evaluation of lower dose schedules for children and adolescents. <ul style="list-style-type: none"> Revised age range for the oldest age group. Revised corresponding objectives, estimands, and endpoints. Revised corresponding SoA and procedures. Revised details in the statistical methods sections. Added flexibility for Visit 5 to be conducted as a telephone visit for the 4500 participants included to enlarge the size of the pediatric safety database, reducing the burden on the participant or participant's parent(s)/legal guardian. Included an exploratory objective to describe the immune response to emerging VOCs. Added the instruction that participants who receive COVID-19 vaccines outside of the study from protocol amendment 5 onwards should be withdrawn to maintain the appropriate assessment of the study intervention. Removed the lifestyle consideration related to strenuous or endurance exercise (potential troponin I testing group only) following regulatory feedback. Updated the appendix for SAE reporting to include guidance on how to report SAEs to Pfizer Safety via an electronic data collection tool.
Amendment 4	29 Sep 2021	<ul style="list-style-type: none"> Revised the success criterion for the efficacy hypotheses to the lower limit of 95% CI >30, in response to regulatory feedback. Added Section 1.1.1, requiring the avoidance of strenuous or endurance exercise 4 days prior to Visit 1 through Visit 1 and from Visit 2 through Visit 3 for the potential troponin I testing subset. Clarified that Phase 2/3 selected-dose participants who originally received active vaccine and are unblinded before Visit 5 will complete the original SoA (Section 1.3.3) before transitioning to the SoA in Section 1.3.3.1.
Amendment 3	10 Sep 2021	<ul style="list-style-type: none"> Updated to allow an additional 2250 Phase 2/3 selected-dose participants <5 years of age, to enlarge the size of the pediatric safety database. This has resulted in the total number of participants in this portion of the study increasing to approximately 9000 participants. Included blood draws, procedures, and objectives for potential troponin I testing in participants ≥5 to <12 and ≥12 to <16 years. Added the rationale for collecting serum samples for potential troponin I testing.

Document History		
Document	Version Date	Summary and Rationale for Changes
		<ul style="list-style-type: none"> Revised an objective and corresponding endpoint to describe severe COVID-19 cases in participants in the selected-dose portion of the study. Clarified the process for participants who become eligible for receipt of BNT162b2 or another COVID-19 vaccine prior to Visit 5 (6-month follow-up visit). Added a second definition of symptoms of severe COVID-19 disease per the CDC definition. Clarified instructions on how to unblind participants at the 6-month follow-up visit. Updated information on the recording of nonstudy vaccination and concomitant medications.
Amendment 2	06 Aug 2021	<ul style="list-style-type: none"> Made the following updates in response to commitments made to CBER concerning myocarditis and pericarditis: <ul style="list-style-type: none"> Insertion of additional row in risk assessment table in risk assessment section. Addition of myocarditis and pericarditis in Adverse Events of Special Interest section. Addition of a procedure to any visit that occurs sooner than 1 month after any vaccination. Addition of an unplanned visit to capture data pertaining to myocarditis and pericarditis. Revised protocol title to reflect the changes in age and dose evaluation. Updated to allow an additional 2250 Phase 2/3 selected-dose participants to enlarge the size of the pediatric safety database. Added Phase 1/2/3 evaluation of lower dose levels for children and young adults with corresponding objectives. Revised the order of Visit 1 activities to clarify when procedures should be conducted in relation to study intervention administration when the visit occurs over 2 consecutive days. Added updates and reformatted activities in the SoA. Removed the requirement to conduct a potential COVID-19 convalescent visit following each potential COVID-19 illness visit. The collection of the blood sample was to support an exploratory endpoint, which will be addressed with external data and thereby reduce burden to participants and caregivers. Added a country-specific appendix that allows flexibility to conduct scheduled follow-up visits in the participant's home, ie, site-arranged home health visits, as permitted per local guidelines (applicable to Poland only).
Amendment 1	05 Mar 2021	<ul style="list-style-type: none"> Added 2 age groups to the study: participants ≥ 2 to < 5 years and ≥ 6 months to < 2 years of age, to also study safety and immunogenicity in these age groups.

Document History		
Document	Version Date	Summary and Rationale for Changes
		<ul style="list-style-type: none"> Updated efficacy objectives to apply across ages in which immunobridging has been successful, if 22 cases are accrued. Made updates to match Pfizer's response to 04 February 2021 CBER comments regarding this study, ie: <ul style="list-style-type: none"> Exclusion criterion 3 applied to all study participants rather than just to Phase 1 participants. References to "noninferiority" updated to "immunobridging." Made additions to the exclusion criteria for previous or current diagnosis of MIS-C. Added to the exclusion criteria receipt of any passive antibody therapy specific to COVID-19 within 90 days prior to enrollment. Specified that placebo recipients who decline BNT162b2 will be followed for 24 months (Visits X and Y). Temporary delay of study intervention criteria regarding nonstudy vaccination updated to be most permissive, ie, to allow easier scheduling around childhood routine vaccinations. Added the following symptoms as prompts to complete the COVID-19/MIS-C illness e-diary: <ul style="list-style-type: none"> Inability to eat/poor feeding in participants <5 years of age; Abdominal pain; Hospitalization due to confirmed COVID-19 infection. Following updates made to the first confirmed COVID-19 case definition to accommodate inclusion of participants <5 years of age: <ul style="list-style-type: none"> Definition of diarrhea added. Inability to eat/poor feeding in participants <5 years of age added as an additional symptom. Definition of SARS-CoV-2-related hospitalization added. RR and HR required to meet the SARS-CoV-2-related severe case definition specified by participant age. Table 4 inserted. Added that cell-mediated immune responses will be described following isolation of PBMCs in a subset of Phase 2/3 participants ≥ 10 years of age. Corresponding visit (Visit 3) added approximately 7 days after Dose 2.
Original protocol	05 Feb 2021	N/A

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.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children.

Rationale

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. On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now rapidly spreading worldwide. Children have been affected by both the primary COVID-19 disease and the less common secondary inflammatory complications, including MIS-C.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19 in participants under 16 years of age. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

A Phase 1/2/3 study (C4591001) is currently being conducted in healthy individuals 12 years of age and older to investigate the safety, tolerability, immunogenicity, and efficacy of the prophylactic BNT162 vaccine candidates against COVID-19. The vaccine candidate selected for evaluation in the C4591001 Phase 2/3 study is BNT162b2 at a 30-µg dose level. The vaccine is administered as 2 doses approximately 21 days apart. On 18 November 2020, the primary efficacy analysis results were announced, which demonstrated BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose; 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group. Safety data from approximately 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 µg in participants 16 years of age and older. 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. On 10 May 2021, the US FDA issued an EUA for use in individuals 12 through 15 years of age. Other countries have also granted EUA or other authorization/approval for this age group (eg, EMA, UK, Switzerland, and the Philippines). BNT162b2 was approved by the FDA on 23 August 2021 to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

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This Phase 1/2/3 study (C4591007) will initially evaluate up to 3 dose levels of BNT162b2 in up to 3 age groups (participants ≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years of age) for safety, tolerability, immunogenicity, and efficacy (depending on successful immunobridging and accrual of a sufficient number of cases). Phase 1 includes the dose-finding portion. Initiation of dose finding in participants ≥ 5 to <12 years of age is based on acceptable blinded safety data demonstrated in 2260 12- through 15-year-olds at the 30- μg dose level in the C4591001 study. The Phase 2/3 BNT162b2 dose level to be used in each age group in this study will be selected based on the Phase 1 safety, tolerability, and immunogenicity data from the same age group. Phase 2/3 (referred to as the selected-dose portion of the study) includes an immunobridging analysis of immune responses in participants within each age group (participants ≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years of age) to those in participants 16 to 25 years of age in the Phase 3 C4591001 efficacy study. Safety, tolerability, and efficacy (depending on successful immunobridging and accrual of a sufficient number of cases) will also be evaluated in Phase 2/3 of this study.

The authorized dose of BNT162b2 in adolescents and young adults 12 years of age and older is 30 μg , whereas the following doses were selected in the ongoing C4591007 Phase 2/3 portion: 10 μg in participants ≥ 5 to <12 years of age and 3 μg in participants 6 months to <5 years of age.

The Phase 2/3 BNT162b2 dose schedule will be selected based on the Phase 1 assessments. The Phase 2/3 part will assess immunobridging of immune responses in participants within each age group to participants in the 30- μg Phase 3 C4591001 efficacy study. Immunobridging criteria comparing participants ≥ 6 months to <2 years of age (3- μg dose) to participants 16 to 25 years of age were met both for the GMR and for seroresponse; however, these criteria were not met for participants ≥ 2 to <5 years of age. Given the emerging data in individuals 16 years of age and older that a third dose may extend high levels of protection, including against the Omicron variant, a third dose may optimally protect individuals ≥ 6 months to <2 years of age and ≥ 2 to <5 years of age from COVID-19. Ongoing safety assessments in these 2 age groups continue to show a favorable safety profile.

In addition, a third dose at least 6 months after the second dose will also be incorporated for participants who are ≥ 5 to <12 years of age.

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

Elevated troponin I level may be an indicator of subclinical myocarditis. If testing of troponin I levels in individuals who did not receive BNT162b2 indicates that troponin I level could be a reliable indicator of potential subclinical myocarditis, obtaining serum samples for potential troponin I testing in an additional group of asymptomatic participants during the period of increased risk of clinical myocarditis may help characterize the absence/presence and frequency of subclinical myocarditis.

On 29 October 2021, the US FDA issued an EUA for use in individuals ≥ 5 to <12 years of age. Enrollment of ≥ 5 to <12 -year-olds was completed at the time of this EUA. Age-eligible participants were unblinded and if administered placebo were offered active immunization. On 17 May 2022, the US FDA expanded the EUA authorizing a booster dose for administration to individuals ≥ 5 to <12 years of age at least 5 months after completion of a primary series of BNT162b2. On 17 June 2022, the US FDA issued the EUA for a primary series of 3 doses of BNT162b2 in children 6 months through 4 years of age, in which the initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose. Per the protocol, age-eligible participants were unblinded and if they received placebo were offered active immunization. Approximately 5800 total participants 6 months to <5 years were enrolled (~ 3600 total participants 2 to <5 years; ~ 2200 total participants 6 months to <2 years) by August 2022 when the enrollment stopped. A recommendation issued by the FDA on 30 June 2022 described the need to modify existing vaccines to address circulating variants and requested that manufacturers begin clinical trials with modified vaccines containing an Omicron BA.4/BA.5 component. On 12 October 2022, the US FDA amended the EUA for bivalent BNT162b2 (original/Omi BA.4/BA.5) for use as a single booster dose for the age group of ≥ 5 to <12 years for administration at least 2 months following the completion of a primary or booster vaccination. Additionally, on 08 December 2022, the US FDA issued the EUA for bivalent BNT162b2 (original/Omi BA.4/BA.5) for use as a third dose of the 3-dose primary series for individuals 6 months through 4 years of age (3- μ g dose level). On 14 March 2023, the US FDA amended the EUA of bivalent BNT162b2 (original/Omi BA.4/BA.5) to provide for a single booster dose in children 6 months through 4 years of age at least 2 months after completion of the primary vaccination with 3 doses of monovalent BNT162b2.

Overall Design

This is a Phase 1/2/3 study in healthy children.

Dependent upon safety and/or immunogenicity data generated during the course of this study, and the resulting assessment of benefit-risk, the safety, tolerability, and immunogenicity of BNT162b2 in participants <6 months of age may subsequently be evaluated. Participants will range from ≥ 6 months to <16 years of age, with different dose levels assessed in each group.

Dose Levels for Each Age Group in the Phase 1 and Phase 2/3 Dose-Finding/Selected-Dose Evaluations and Obtaining Serum Samples for Potential Troponin I Testing

Phase 1 Open-Label Dose-Finding Evaluation^a					
	≥6 Months to <2 Years	≥2 to <5 Years	≥5 to <12 Years	≥12 to <16 Years	Total
Dose level(s)	3 µg	3/10 µg	10/20/30 µg		
Participants	16 ^b	16/32 ^b	16/16/16 ^c		112
Phase 2/3 Observer-Blinded, Placebo-Controlled Selected-Dose Evaluation^a					
Dose level	3 µg	3 µg	10 µg	30 µg	
Participants (Planned Enrollment)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	Any participant who turns 12 years of age during the course of the study will be offered the 30-µg dose level for all subsequent doses	13,500
	≥6 Months to <2 Years	≥2 to <5 Years	≥5 to <12 Years	≥12 to <16 Years	Total
Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing					
Planned dose level			10 µg	30 µg	
Participants (Planned Enrollment)			750 (active 500; placebo 250)	500 (active 500; placebo 0)	1250
Phase 2/3 total by age group (Planned Enrollment)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	5250 (active 3500; placebo 1750)	500 (active 500; placebo 0)	14,750

- The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination.
- Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
- Actual number of participants recruited in the ≥5 to <12 years age group. Dose 1: 16 out of 16 received 30-µg dose level; Dose 2: 4 out of 16 received 30-µg dose level and 12 of 16 received 10-µg dose level.

Phase 1

Dose-finding: Is the open-label dose-finding portion of the study that will evaluate safety, tolerability, and immunogenicity of BNT162b2 administered on a 2-dose (separated by approximately 21 days) schedule in up to 3 age groups (participants ≥5 to <12 years, ≥2 to <5 years, and ≥6 months to <2 years of age).

Dose finding is being initiated in this study in participants ≥5 to <12 years of age based on the acceptable blinded safety assessment of the 30-µg dose in 12- to 15-year-olds in the C4591001 study.

The purpose of Phase 1 is to identify preferred dose level(s) of BNT162b2 from up to 3 different dose levels in each age group.

Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose.

Update as part of protocol amendment 6: All participants will receive a third dose of BNT162b2. For participants ≥ 6 months to < 5 years, the third dose will occur at least 8 weeks after the second dose. In participants ≥ 5 to < 12 years, the third dose will occur at least 6 months after the second dose. The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the third dose of BNT162b2 will be based on age at the time of vaccination: participants < 5 years of age at the time of the third dose will receive the 3- μg dose level, participants ≥ 5 to < 12 years of age at the time of the third dose will receive the 10- μg dose level, and participants ≥ 12 years of age at the time of the third dose will receive the 30- μg dose level.

Participants will have blood drawn prior to both Dose 1 and Dose 2 and 7 days after Dose 2 to assess immunogenicity to determine the selected BNT162b2 dose level for Phase 2/3. Participants will also have blood drawn prior to Dose 3 and 1, 6, and 12 months after Dose 3 (As of 01 September 2022, a blood sample is no longer required at 1, 6, and 12 months after Dose 3).

Phase 2/3

Selected-dose: Is the portion of the study that will evaluate the safety, tolerability, and immunogenicity in each age group at the selected dose level from the Phase 1 dose-finding portion of the study. Efficacy will be evaluated within or across age groups in which immunobridging is successful, depending on accrual of a sufficient number of cases in those age groups.

Participants will have blood drawn at baseline prior to Dose 1 (for all participants) and 6 months after Dose 2 (for participants ≥ 5 to < 12 years of age only, not in safety expansion). Immunobridging to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at (1) baseline and 1 month after Dose 2 and (2) baseline and 1 month after Dose 3. The persistence of the immune response will be based on immunogenicity data collected in participants at (1) baseline and 1 and 6 months after Dose 2 and (2) baseline and 1, 6, 12, and 18 months after Dose 3 (As of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8). In addition, efficacy against confirmed COVID-19 infection will also be assessed.

At designated US sites, an additional optional whole blood sample of approximately 10 mL will be obtained prior to Dose 1 and at 7 days and 6 months after Dose 2 from up to approximately 60 participants ≥ 10 years of age. Additional samples will be obtained prior to Dose 3 and 1 month after Dose 3 (original BNT162b2 group only). These samples will be used on an exploratory basis to investigate the postvaccination cell-mediated immune response at these time points.

At the 6-month follow-up visit, all participants will be unblinded. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to the 6-month follow-up visit (Visit 5 or 405) (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo will have the opportunity to receive BNT162b2 (10 μ g or 3 μ g) based on age at the time of vaccination prior to the 6-month follow-up visit (Visit 5 or 405).

Update as part of protocol amendment 6: All participants will receive a third dose of BNT162b2. For participants ≥ 6 months to < 5 years, the third dose will occur at least 8 weeks after the second dose. In participants ≥ 5 to < 12 years, the third dose will occur at least 6 months after the second dose (updated to at least 5 months for US participants as part of protocol amendment 8). The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants < 5 years of age at the time of the second/third dose will receive the 3- μ g dose level, participants ≥ 5 to < 12 years of age at the time of the second/third dose will receive the 10- μ g dose level, and participants ≥ 12 years of age at the time of the second/third dose will receive the 30- μ g dose level.

Participants enrolled in the ≥ 2 to < 5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥ 5 to < 12 years age group (ie, third dose administered at least 6 months after the second dose, updated to at least 5 months for US participants as part of protocol amendment 8).

Obtaining serum samples for potential troponin I testing: If testing of troponin I levels in individuals who did not receive BNT162b2 indicates that troponin I level could be a reliable indicator of potential subclinical myocarditis, obtaining serum samples for potential troponin I testing during the period of increased risk of clinical myocarditis may help characterize the absence/presence and frequency of subclinical myocarditis. To assess, an additional group of participants will be included: ≥ 5 to < 12 years: 750 participants randomized 2:1 to receive BNT162b2 10 μ g or placebo, and 500 participants ≥ 12 to < 16 years of age: open-label receipt of BNT162b2 30 μ g.

Update as part of protocol amendment 7: All participants will receive a third dose of BNT162b2. For all participants (≥ 5 to <12 and ≥ 12 to <16 years of age), the third dose will occur at least 5 months after Dose 2.

The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants ≥ 5 to <12 years of age at the time of the second/third dose will receive the 10- μg dose level, and participants ≥ 12 years of age at the time of the second/third dose will receive the 30- μg dose level.

As of protocol amendment 8, since the study is now fully unblinded with no control arm, making it observational in nature and with increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial, and following agreement with the FDA and EMA, the study will be concluded early. Following approval of protocol amendment 8, active study participants will be informed of the early completion of the study, and further data collection will cease 6 months after the third dose of BNT162b2.

Number of Participants

Phase 1: Open-Label Dose-Finding

Phase 1 is an open-label study that will consist of up to 3 different dose levels in each age group, with a minimum of 16 participants per dose level (total of 144 participants) for the dose-finding evaluation.

Phase 1 Dose-Finding Participants				
Age Group	Total	Up to 3 Dose Levels of BNT162b2 ^a	Active	Placebo
≥ 5 to <12 Years	48	16/16/16	16	N/A
≥ 2 to <5 Years	48	16/16/16	16	N/A
≥ 6 Months to <2 years	48	16/16/16	16	N/A

a. A dose level may be expanded to enroll more than 16 participants per dose level.

Phase 2/3: Safety, Tolerability, Immunogenicity, and Efficacy

Selected-dose: Is the portion of the study that will evaluate the safety, tolerability, and immunogenicity of the selected dose level in each age group from the Phase 1 dose-finding portion of the study, with a total of approximately 13,500 participants, as an additional 4500 participants will be included to further enlarge the size of the pediatric safety database. Participants will be randomized in a 2:1 ratio to receive active vaccine or placebo.

Approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) randomized in each age group in this phase will contribute to the immunobridging analysis at 1 month after Dose 2 and 100 participants in the active vaccine group will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2 and 6, 12, and 18 months after Dose 3 (as of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8). These participants will be enrolled from across study sites to ensure this subset is representative of the whole study.

Approximately 250 participants (200 in the active vaccine group and 50 in the placebo group) randomized in each younger age group (≥ 6 months to < 2 years and ≥ 2 to < 5 years of age) in this phase will contribute to the immunobridging analysis at 1 month after Dose 3 (participants who are currently enrolled prior to protocol amendment 6).

For the persistence time points of 6 and 12 months after Dose 3, approximately 100 participants from each age group enrolled prior to protocol amendment 6 in the original BNT162b2 group will have an immunogenicity blood draw in order to contribute to the analysis (as of 20 October 2022, a blood sample is no longer required at 6 and 12 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8).

All approximately 13,500 participants will contribute to the VE analysis. Efficacy will be evaluated for ≥ 5 to < 12 years and the combination of ≥ 6 months to < 2 years and ≥ 2 to < 5 years of age if immunobridging is successful, depending on accrual of a sufficient number of cases in those age groups.

Phase 2/3 Selected-Dose Participants Enrolled Before Protocol Amendment 6 – Blood Draws for Immunogenicity/Efficacy Assessments									
	All Age Groups			≥ 5 to < 12 Years of Age			≥ 2 to < 5 Years and ≥ 6 Months to < 2 Years of Age ^a		
	Total	Active	Placebo	Total	Active	Placebo	Total	Active	Placebo
Baseline blood draw (Visit 1)	9000	6000	3000	4500	3000	1500	2250	1500	750
1 Month after Dose 2 (Visit 4)	1350	900	450	450	300	150	450	300	150
6 Months after Dose 2 (Visit 5)	Up to 2250	Up to 1500	Up to 750	Up to 2250	Up to 1500	Up to 750	N/A	N/A	N/A
Dose 3	7500	6000	Up to 1500	3000	3000	N/A	2250	1500	Up to 750
1 Month after Dose 3	7500	6000	Up to 1500	3000	3000	N/A	2250	1500	Up to 750
6 Months after Dose 3 ^b	300	300	N/A	100	100	N/A	100	100	N/A
12 Months after Dose 3 ^b	300	300	N/A	100	100	N/A	100	100	N/A

Note: Because of operational considerations, the numbers in these age groups may vary.

- Number of participants shown is for each of these 2 younger age groups.
- This assessment is not required as of 20 October 2022.

Enrolled from protocol amendment 6 onwards: Among participants ≥ 6 months to < 2 years and ≥ 2 to < 5 years of age enrolled after protocol amendment 6, approximately 300 participants (200 in the active vaccine group and 100 in the placebo group) randomized in each age group will have an immunogenicity blood draw at 1 month after Dose 3 and approximately 100 participants in the original BNT162b2 group will have an immunogenicity blood draw at 6, 12, and 18 months after Dose 3 (as of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3).

Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards – Blood Draws for Immunogenicity/Efficacy Assessments										
	All Age Groups			≥ 6 Months to < 2 Years of Age			≥ 2 to < 5 Years of Age			
		Total	Active	Placebo	Total	Active	Placebo	Total	Active	Placebo
Baseline blood draw	4500	3000	1500	2250	1500	750	2250	1500		750
1 Month after Dose 3 ^a	600	400	200	300	200	100	300	200		100
6 Months after Dose 3 ^b	200	200	N/A	100	100	N/A	100	100		N/A
12 Months after Dose 3 ^b	200	200	N/A	100	100	N/A	100	100		N/A
18 Months after Dose 3 ^b	200	200	N/A	100	100	N/A	100	100		N/A

Note: Because of operational considerations, the numbers in these age groups may vary.

- Unblinding had been initiated based on the EUA for primary series received on 17 June 2022 for ages 6 months to < 5 years, resulting in placebo recipients being unblinded. No further blood draws for this group will be required.
- These assessments are no longer required as of 20 October 2022.

All participants will contribute to the safety, tolerability, and efficacy assessments.

Phase 2/3 Selected-Dose Participants – Safety and Tolerability/Efficacy Assessments			
Age	Total	Active	Placebo
≥ 5 to < 12 Years	4500	3000	1500
≥ 2 to < 5 Years	4500	3000	1500
≥ 6 Months to < 2 Years	4500	3000	1500
All age groups (Planned Enrollment)	13,500	9000	4500

Obtaining serum samples for potential troponin I testing: 750 participants ≥ 5 to < 12 years of age (randomized 2:1 to receive BNT162b2 10 μg or placebo) and 500 participants ≥ 12 to < 16 years of age (open-label receipt of BNT162b2 30 μg).

Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing – Blood Draws for Potential Troponin I Level Evaluation									
	Sum of Age Groups Currently Included in Potential Troponin I Testing Within Protocol			≥5 to <12 Years of Age Placebo-Controlled (2:1 Randomization)			≥12 to <16 Years of Age Open-Label		
	Total	Active	Placebo	Total	Active	Placebo	Total	Active	Placebo
Baseline blood draw	1250	1000	250	750	500	250	500	500	N/A
4 Days after Dose 2	1250	1000	250	750	500	250	500	500	N/A
4 Days after Dose 3	1250	1250	N/A	750	750	N/A	500	500	N/A

Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing – Safety and Tolerability Assessments		
Total	Active	Placebo
1250	1000	250

Intervention Groups and Duration

Phase 1

Dose-finding: Dosing will begin at the low-dose level in participants ≥5 to <12 years of age. Controlled enrollment will be required for the first dose level studied in each age group. Only a limited number of participants (~4) are dosed before allowing dosing in the remaining participants (~12) in the same age and dose-level group. The IRC will review safety data (e-diary and AE) acquired up to 7 days after Dose 1 for the low-dose level group; upon confirmation of an acceptable safety assessment by the IRC:

- Dosing may commence at the mid-dose level in the same age group, and
- Dosing may commence at the low-dose level in participants ≥2 to <5 years of age.

The same process will be followed when moving up dose levels in each age group, and when progressing between age groups at the low-dose level as shown in [Section 1.2](#). Dosing may commence at the low-dose level in participants ≥6 months to <2 years of age after IRC review of safety data (e-diary and AE) acquired up to 7 days after Dose 1 at the low-dose level from participants ≥2 to <5 years of age.

In each age group, if the low-dose level is considered not acceptable based on safety assessment after Dose 1, the mid-dose level or high-dose level will not commence. In this case, an optional lower dose level may commence. Dependent on the results obtained, dose level(s) may be omitted. In each age group, if the mid-dose level is considered not acceptable based on safety assessment after Dose 1, the high-dose level will not commence.

Based on safety assessments, the second dose may be given at a lower dose level.

Duration of the dose-finding portion of the study: Participants are expected to participate for approximately 19 months.

Phase 2/3

Selected-dose: Progression of each age group into Phase 2/3 will occur independently; it is therefore possible that each age group may not start Phase 2/3 concurrently and the dose level selected for Phase 2/3 may differ by age group. For each age group to proceed to Phase 2/3, safety, tolerability, and immunogenicity data from 7 days after Dose 2 for the selected vaccine dose level in that age group from Phase 1 will be confirmed to be acceptable.

Duration of the selected-dose portion of the study:

Protocol amendment 8 will truncate participants' study involvement to allow early completion of the study without the need to complete all study visits as per the SoA.

- Participants ≥ 6 months to < 12 years old enrolled before protocol amendment 6 who originally received BNT162b2 are expected to participate for approximately 19 months.
- Participants ≥ 6 months to < 12 years old that cross over (from placebo to active vaccine) before protocol amendment 6 who originally received placebo are expected to participate for approximately 25 months.
- Participants ≥ 6 months to < 5 years old enrolled from protocol amendment 6 onwards who originally received BNT162b2 are expected to participate for approximately 21 months.
- Participants ≥ 6 months to < 5 years old that cross over (from placebo to active vaccine) after protocol amendment 6 who originally received placebo are expected to participate for approximately 21 months.

Obtaining serum samples for potential troponin I testing: Progression of each age group will occur concurrently.

Duration of obtaining serum samples for potential troponin I testing: Participants are expected to participate for up to a maximum of approximately 13 months.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose finding in Phase 1.

An external DMC will review cumulative unblinded data and monitor vaccine safety throughout the study.

Statistical Methods

Immunobridging of the immune response to prophylactic BNT162b2 after a 2-dose series in participants within each age group to the response in participants in the comparator group from Phase 2/3 of the C4591001 study will be assessed separately for each age group and based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin and the difference in percentages of participants with seroresponse using a 10% margin.

Within each age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially in the order specified. Immunobridging success based on GMR will be declared if the lower limit of the 95% CI for the GMR (each age group to the comparator age group from the C4591001 study) is >0.67 and the point estimate of the GMR is ≥ 0.8 . Immunobridging success based on the seroresponse difference will be declared if the lower limit of the 95% CI for the difference in percentages of participants with seroresponse is $>-10\%$. Since seroresponse is not directly linked to an antibody level associated with protection against COVID-19, if the seroresponse endpoint nearly misses the noninferiority criteria, the totality of evidence will be evaluated, including RCDCs and the proportion of participants with neutralizing titers \geq LLOQ.

A sample size of 225 evaluable participants in each age group evaluated in this study and the corresponding comparator group from the C4591001 study will provide a power of 90.4% and 92.6% to declare immunobridging success after a 2-dose series based on GMR and seroresponse difference, respectively. The immunogenicity data from the 300 active vaccine recipients in approximately 450 participants randomized in each age group, in the Phase 2/3 selected-dose portion of the study, will be used for the 2-dose series immunobridging assessment.

Immunobridging of the immune response to prophylactic BNT162b2 after a 3-dose series in participants ≥ 2 to <5 years and ≥ 6 months to <2 years of age to the immune response in participants in the comparator group from Phase 2/3 of the C4591001 study will be evaluated in a similar way as for the 2-dose series. For those participants who are currently enrolled (prior to protocol amendment 6), a sample size of 130 evaluable participants in each age group evaluated in this study and the corresponding comparator group from the C4591001 study will provide a power of 93.3% and 90.4% to show immunobridging after a 3-dose series based on GMR and seroresponse difference, respectively. A sample of approximately 200 participants who received 3 doses of BNT162b2 in each younger age group and the same number of participants 16 to 25 years of age who received 2 doses of BNT162b2 from Phase 2/3 of the C4591001 study will be selected as the immunobridging subset for this evaluation.

The other immunogenicity objectives will be evaluated descriptively by GMT, GMFR, and the associated 95% CIs for SARS-CoV-2 neutralizing titers at the various time points.

The secondary efficacy objectives are to evaluate VE, defined as $100 \times (1 - \text{IRR})$, against the confirmed COVID-19 illness, in each of the 2 age groups (≥ 5 to < 12 years: after a 2-dose series, and ≥ 6 months to < 2 years and ≥ 2 to < 5 years combined: after a 3-dose series). IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With the assumption of a true VE of 80%, 21 cases will provide 77% power to conclude true VE $> 30\%$. Hypothesis testing for the specific age groups (≥ 5 to < 12 years; ≥ 6 months to < 2 years and ≥ 2 to < 5 years combined) will be conducted only if at least 21 cases are accrued in those age groups.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine and age group. A 3-tier approach will be used to summarize AEs during the blinded follow-up period in the Phase 2/3 selected-dose portion of the study.

1.2. Schema

Phase 1 Dose-Finding and Phase 2/3 Selected-Dose Evaluation

≥5 to <12 Years		≥2 to <5 Years		≥6 Months to <2 Years
<u>Phase 1</u> <u>All participants receive BNT162b2</u>		<u>Phase 1</u> <u>All participants receive BNT162b2</u>		<u>Phase 1</u> <u>All participants receive BNT162b2</u>
Low-dose level (n=16)^a		Low-dose level (n=16)^a		Low-dose level (n=16)^a
IRC ↓	IRC ^b	IRC ↓	IRC ^b	IRC ↓
Mid-dose level (n=16)	→	Mid-dose level (n=16)	→	Mid-dose level (n=16)
IRC ↓		IRC ↓		IRC ↓
High-dose level (n=16)		High-dose level (n=16)		High-dose level (n=16)
IRC ^c ↓		IRC ^c ↓		IRC ^c ↓
<u>Phase 2/3</u> <u>Participants randomized to receive</u> <u>2:1 BNT162b2: placebo</u>		<u>Phase 2/3</u> <u>Participants randomized to receive</u> <u>2:1 BNT162b2: placebo</u>		<u>Phase 2/3</u> <u>Participants randomized to receive</u> <u>2:1 BNT162b2: placebo</u>

- In each age group, if the low-dose level is considered not acceptable based on safety assessment after Dose 1, the mid-dose level or high-dose level will not commence. In this case, an optional lower dose level may commence.
- The IRC will review safety data (e-diary and AE) acquired up to 7 days after Dose 1 in the low-dose-level group, and dosing may commence at the low-dose level in the next age group based upon confirmation of an acceptable safety assessment at this review.
- IRC choice of dose level for each age group. Dependent on safety, tolerability, and immunogenicity data from 7 days after Dose 2 in each age group.

Dose Levels for Each Age Group in the Phase 1 and Phase 2/3 Dose-Finding/Selected-Dose Evaluations and Obtaining Serum Samples for Potential Troponin I Testing

Phase 1 Open-Label Dose-Finding Evaluation^a					
	≥6 Months to <2 Years	≥2 to <5 Years	≥5 to <12 Years	≥12 to <16 Years	Total
Dose level	3 µg	3/10 µg	10/20/30 µg		
Participants	16 ^b	16/32 ^b	16/16/16 ^c		112
Phase 2/3 Observer-Blinded, Placebo-Controlled Selected-Dose Evaluation^a					
Dose level	3 µg	3 µg	10 µg	30 µg	
Participants (Planned Enrollment)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	Any participants who turn 12 years old during the course of the study will be offered the 30-µg dose level for all subsequent doses	13,500
Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing					
Planned dose level			10 µg	30 µg	
Participants (Planned Enrollment)			750 (active 500; placebo 250)	500 (active 500; placebo 0)	1250
	≥6 Months to <2 Years	≥2 to <5 Years	≥5 to <12 Years	≥12 to <16 Years	Total
Phase 2/3 total by age group (Planned Enrollment)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	5250 (active 3500; placebo 1750)	500 (active 500; placebo 0)	14,750

- The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination.
- Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
- Actual number of participants recruited in the ≥5 to <12 years age group. Dose 1: 16 out of 16 received 30-µg dose level; Dose 2: 4 out of 16 received 30-µg dose level and 12 of 16 received 10-µg dose level.

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 information 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 participant.

1.3.1. Phase 1 Dose-Finding Portion

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that COVID-19/MIS-C symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19/MIS-C illness rather than vaccine reactogenicity. For details, see [Section 8.13](#).

From protocol amendment 6, the SoA includes a third dose applicable to all enrolled participants. For participants ≥ 6 months to < 5 years of age, the third dose will occur at least 8 weeks after Dose 2. For participants ≥ 5 to < 12 years of age, the third dose will occur at least 6 months after Dose 2.

The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the third dose of BNT162b2 will be based on age at the time of vaccination: participants < 5 years of age at the time of the third dose will receive the 3- μg dose level, participants ≥ 5 to < 12 years of age at the time of the third dose will receive the 10- μg dose level, and participants ≥ 12 years of age at the time of the third dose will receive the 30- μg dose level.

Phase 1 Dose-Finding Portion										
Visit Number	1	2	3	4	5	5A	5B	5C	6	Unplanned
Visit Description	Dose 1 ^a	Dose 2	7 Day Follow-up Visit (1 Week After Dose 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	Dose 3	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^b	Potential COVID-19/MIS-C Illness Visit ^{b,c}
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	≥5 to <12 Y: At Least 175 Days After Visit 2 OR ≥6 M to <5 Y: At Least 60 Days After Visit 2	28 to 35 Days After Visit 5A	175 to 189 Days After Visit 5A	350 to 378 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^d	Telephone	Clinic ^e	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Obtain informed consent and assent (if appropriate)	X					X				
Assign participant number	X									
Obtain demography and significant medical history data	X									
Confirm use of contraceptives (if appropriate)	X	X	X	X		X	X			
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X	X	X	X	X
Confirm eligibility	X	X				X				
Review temporary delay criteria	X	X				X				
Measure vital signs (including body temperature)	X	X				X				

Phase 1 Dose-Finding Portion										
Visit Number	1	2	3	4	5	5A	5B	5C	6	Unplanned
Visit Description	Dose 1 ^a	Dose 2	7 Day Follow-up Visit (1 Week After Dose 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	Dose 3	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^b	Potential COVID-19/ MIS-C Illness Visit ^{b,c}
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	≥5 to <12 Y: At Least 175 Days After Visit 2 OR ≥6 M to <5 Y: At Least 60 Days After Visit 2	28 to 35 Days After Visit 5A	175 to 189 Days After Visit 5A	350 to 378 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^d	Telephone	Clinic ^e	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Perform physical examination (including height and weight) ^f	X	X				X				
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X				X				
Obtain randomization number and study intervention allocation	X									
Obtain anterior nasal swab	X	X				X				X
Collect blood sample for immunogenicity	~5 mL	~5 mL	~5 mL			~5 mL	~5 mL ¹	~5 mL ¹	~5 mL ¹	
Administer study intervention	X	X				X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X				X				

Phase 1 Dose-Finding Portion										
Visit Number	1	2	3	4	5	5A	5B	5C	6	Unplanned
Visit Description	Dose 1 ^a	Dose 2	7 Day Follow-up Visit (1 Week After Dose 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	Dose 3	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^b	Potential COVID-19/MIS-C Illness Visit ^{b,c}
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	≥5 to <12 Y: At Least 175 Days After Visit 2 OR ≥6 M to <5 Y: At Least 60 Days After Visit 2	28 to 35 Days After Visit 5A	175 to 189 Days After Visit 5A	350 to 378 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^d	Telephone	Clinic ^e	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X					X				
Provide a thermometer and caliper (measuring) device	X									
Reactivate reactogenicity e-diary		X				X				
Ensure the participant's parent(s)/legal guardian/has a caliper device and thermometer		X				X				
Ask the participant's parent(s)/legal guardian to complete e-diary and ensure the participant's parent(s)/legal guardian remains comfortable with chosen e-diary platform	X	X				X				

Phase 1 Dose-Finding Portion										
Visit Number	1	2	3	4	5	5A	5B	5C	6	Unplanned
Visit Description	Dose 1 ^a	Dose 2	7 Day Follow-up Visit (1 Week After Dose 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	Dose 3	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^b	Potential COVID-19/ MIS-C Illness Visit ^{b,c}
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	≥5 to <12 Y: At Least 175 Days After Visit 2 OR ≥6 M to <5 Y: At Least 60 Days After Visit 2	28 to 35 Days After Visit 5A	175 to 189 Days After Visit 5A	350 to 378 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^d	Telephone	Clinic ^e	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	↔	↔	↔			↔				
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			X			
Collect AEs ^g	X	X	X	X		X	X			X
Collect SAEs ^h	X	X	X	X	X	X	X	X		X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application									X ⁱ	

Phase 1 Dose-Finding Portion										
Visit Number	1	2	3	4	5	5A	5B	5C	6	Unplanned
Visit Description	Dose 1 ^a	Dose 2	7 Day Follow-up Visit (1 Week After Dose 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	Dose 3	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^b	Potential COVID-19/MIS-C Illness Visit ^{b,c}
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	≥5 to <12 Y: At Least 175 Days After Visit 2 OR ≥6 M to <5 Y: At Least 60 Days After Visit 2	28 to 35 Days After Visit 5A	175 to 189 Days After Visit 5A	350 to 378 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^d	Telephone	Clinic ^e	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Collection of COVID-19/MIS-C-related clinical and laboratory information (including local diagnosis)										X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; M = month(s); MIS-C = multisystem inflammatory syndrome in children; SMS = short message service; Y = year(s).

Phase 1 Dose-Finding Portion										
Visit Number	1	2	3	4	5	5A	5B	5C	6	Unplanned
Visit Description	Dose 1 ^a	Dose 2	7 Day Follow-up Visit (1 Week After Dose 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	Dose 3	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^b	Potential COVID-19/MIS-C Illness Visit ^{b,c}
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	≥5 to <12 Y: At Least 175 Days After Visit 2 OR ≥6 M to <5 Y: At Least 60 Days After Visit 2	28 to 35 Days After Visit 5A	175 to 189 Days After Visit 5A	350 to 378 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^d	Telephone	Clinic ^e	Clinic or Telephone	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth

- The visit may be conducted across 2 consecutive days; if so, please refer to [Section 8.11.1.1](#).
- This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point or prior to potential COVID-19 illness onset.
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.
- If Visit 5A (Dose 3) occurs on or before Visit 5 (6-month follow-up visit after Dose 2), then Visit 5 does not need to be completed.
- A physical examination will include, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey. Height and weight will be collected only at Visit 1.
- Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Refer to [Section 8.3.1](#) for the time period for collecting SAEs.
- This blood sample is not required for participants as of 01 September 2022.
- When protocol amendment 8 is approved and participants are informed of early study completion, the e-diary device return should be arranged by the site.

1.3.2. Phase 2/3 Selected-Dose Portion

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that potential COVID-19/MIS-C symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19/MIS-C illness rather than vaccine reactogenicity. For details, see [Section 8.13](#).

Administration of BNT162b2 to those originally assigned to placebo: At the time of the 6-month follow-up visit, all participants will be unblinded. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to the 6-month follow-up visit (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo will have the opportunity prior to the 6-month follow-up visit to receive BNT162b2 (10 µg or 3 µg) based on age at the time of vaccination. When contacted, the site will conduct a telephone visit to confirm eligibility and, if the participant is eligible and wants to receive BNT162b2 in the event that he or she originally received placebo, the site will unblind the participant's study intervention allocation to determine whether the participant received BNT162b2 or placebo. In either scenario above, if he or she originally received placebo and wants to receive BNT162b2 (10 µg or 3 µg), the participant will move to the SoA in [Section 1.3.2.2](#) if he or she has crossed over to active vaccine prior to protocol amendment 6 or the SoA in [Section 1.3.2.3](#) if he or she is ≥6 months to <5 years old crossing over to active vaccine after protocol amendment 6 for the remaining visits. Participants who originally received BNT162b2 will complete the SoA immediately below (Section 1.3.2) before moving to the SoA in [Section 1.3.2.1](#).

From protocol amendment 6, the SoA includes a third dose applicable to all enrolled participants. For participants ≥6 months to <5 years old, the third dose will occur at least 8 weeks after Dose 2. If the Dose 3 1-month follow-up (Visit 4B) is projected to occur after the planned Visit 5, then Visit 4B should be conducted and Visit 5 should not be conducted. If a ≥6-month-old to <5-year-old participant who originally received BNT162b2 has completed Visit 5, then the participant should complete Visits 4A and 4B before moving to the SoA in [Section 1.3.2.1](#). For participants ≥5 to <12 years of age, the third dose will occur at least 6 months after Dose 2 (updated to at least 5 months for US participants as part of protocol amendment 8).

The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants <5 years of age at the time of the second/third dose will receive the 3- μ g dose level, participants ≥ 5 to <12 years of age at the time of the second/third dose will receive the 10- μ g dose level, and participants ≥ 12 years of age at the time of the second/third dose will receive the 30- μ g dose level.

Participants enrolled in the ≥ 2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥ 5 to <12 years age group (ie, third dose administered at least 6 months after the second dose).

Participants who completed Visit 5 (6-month follow-up visit) and were unblinded to study intervention allocation before protocol amendment 6 will proceed as follows:

- If the participant previously received BNT162b2 and was ≥ 5 to <12 years old at the time of enrollment, the participant should complete Visit 5A and Visit 5B on this schedule (Dose 3 administered at Visit 5A and Dose 3 1-month follow-up at Visit 5B).
- If the participant previously received BNT162b2 and was ≥ 6 months to <5 years old at the time of enrollment, the participant should complete Visit 4A and Visit 4B on this schedule (Dose 3 administered at Visit 4A and Dose 3 1-month follow-up at Visit 4B).
- Participants (≥ 6 months to <12 years old) who originally received placebo who crossed over to the SoA in [Section 1.3.2.2](#) before protocol amendment 6 will receive 3 doses of BNT162b2 at the appropriate dose interval as part of that schedule.

If protocol amendment 6 is implemented before the participant has completed Visit 5, the participant's parent(s)/legal guardian should be offered the consent addendum to receive a blinded third dose. If the participant's parent(s)/legal guardian refuses to sign the consent addendum, the participant should continue to Visit 5 and complete study procedures and unblinding. Following unblinding, the consent addendum should be reoffered. If the participant's parent(s)/legal guardian refuses any further vaccinations, then the participant should be withdrawn having completed the 6-month post-Dose 2 safety follow-up.

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Obtain informed consent and assent (if appropriate)	X				X			X		
Assign participant number	X									
Obtain demography and significant medical history data (including breastfeeding) ⁱ	X	~ ⁱ	~ ⁱ	~ ⁱ	~ ⁱ	~ ⁱ	~ ⁱ			
For participants who are HIV positive, record latest CD4 count and HIV viral load	X			X	X	X	X	X	X	
Confirm use of contraceptives (if appropriate)	X	X	X	X				X	X	
Collect maternal COVID-19 immunization data, for any COVID-19 vaccines given during pregnancy ⁱ	X	~ ⁱ	~ ⁱ	~ ⁱ	~ ⁱ	~ ⁱ	~ ⁱ			

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X	
Collect prohibited medication use		X	X	X	X	X	X	X	X	X
Confirm eligibility	X	X			X			X		
Review and consider eligibility					X			X		
Review temporary delay criteria	X	X			X			X		
Measure vital signs (including body temperature)	X	X			X			X		
Perform physical examination (including height and weight) ^j	X	X			X			X		
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X						X		

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Obtain randomization number and study intervention allocation	X									
Obtain anterior nasal swab	X	X			X			X		X
Collect blood sample for immunogenicity	~5 mL			~5 mL ^k	~5 mL	~5 mL	~5 mL ^l	~5 mL	~5 mL	
Collect blood sample for PBMC isolation ^b	~10 mL		~10 mL				~10 mL	~10 mL	~10 mL	
Administer study intervention	X	X			X			X		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X			X			X		

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X				X			X		
Provide thermometer and caliper (measuring) device	X									
Reactivate reactivity e-diary		X			X			X		
Ensure the participant’s parent(s)/legal guardian has a caliper device and thermometer		X			X			X		

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Ask the participant’s parent(s)/legal guardian to complete e-diary and ensure the participant’s parent(s)/legal guardian remains comfortable with chosen e-diary platform	X	X			X			X		
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	↔	↔								
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X		X			X	
Collect AEs as appropriate ^m	X	X	X	X	X	X		X	X	X

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					<u>Only for Participants >6 Months to <5 Years of Age</u>			<u>Only for Participants >5 to <12 Years of Age</u>		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Collect SAEs as appropriate ^a	X	X	X	X	X	X	X	X	X	X
Unblind the participant and move to either Section 1.3.2.1 , Section 1.3.2.2 , or Section 1.3.2.3 as appropriate ^o							X ^d			

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)										X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; HIV = human immunodeficiency virus; M = month(s); MIS-C = multisystem inflammatory syndrome in children; PBMC = peripheral blood mononuclear cell; SMS = short message service; Y = year(s).

- This visit may be conducted across 2 consecutive dates; if so, please refer to [Section 8.11.2.1](#).
- Applicable at designated sites only for participants ≥10 years of age whose parents/legal guardians have given consent for this additional blood draw.
- For participants ≥6 months to <5 years old, if Visit 4B is projected to occur after the planned Visit 5, then Visit 4B should replace Visit 5.
- Visit 5 and the 6-month post-Dose 2 unblinding may occur via telephone for participants who do not require a clinic visit at Visit 5 (ie, do not require a blood draw). If Visit 4B is projected to occur after the planned Visit 5, unblinding should only occur at Visit 4B after all Visit 4B procedures are completed.
- If Visit 5A (Dose 3) occurs on or before Visit 5 (6-month follow-up visit after Dose 2), then Visit 5 does not need to be conducted. In the US, the Visit 5A Dose 3 will occur at least 140 days after Visit 2.
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.
- This visit can be conducted as a telephone visit for the 4500 participants included as part of protocol amendments 2 (2250 in ≥5- to <12-year-olds) and 3 (2250 in <5-year-olds) to enlarge the size of the pediatric safety database and for participants under 5 years of age at enrollment.

Phase 2/3 Selected-Dose Portion: Participants 6 Months to <12 Years Old Enrolled Before Protocol Amendment 6										
Visit Number	1	2	3	4	4A	4B	5	5A	5B	Unplanned
					Only for Participants >6 Months to <5 Years of Age			Only for Participants >5 to <12 Years of Age		
Visit Description	Dose 1 ^a	Dose 2	1-Week Follow-up Visit ^b	1-Month Follow-up Visit	Dose 3 ≥6 M to <5 Y	Dose 3 1-Month Follow-up Visit ^c	6-Month Follow-up Visit ^d	Dose 3 ≥5 to <12 Y ^e	Dose 3 1-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^f
Visit Window (Days)	Day 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 2	28 to 35 Days After Visit 2	At Least 60 Days After Visit 2	28 to 35 Days After Visit 4A	175 to 189 Days After Visit 2	At Least 175 Days After Visit 2	28 to 35 Days After Visit 5A	Optimally Within 3 Days After Potential COVID-19/ MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone ^g	Clinic	Clinic	Clinic or Telephone ^h	Clinic	Clinic	Clinic or Telehealth

- i. Collection of breastfeeding and maternal COVID-19 immunization data is only applicable to participants ≥6 months to <2 years of age. If not collected at an earlier visit, breastfeeding and maternal COVID-19 immunization data need to be collected (once only). Prior to collection of maternal COVID-19 vaccination data, the biological mother of the participant should sign the Release of Maternal COVID-19 Vaccination Information Form (see [Section 8.17](#)).
- j. A physical examination will include, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey. Height and weight will be collected only at Visit 1.
- k. Approximately 450 randomized participants in each age group will have blood drawn at 1 month after Dose 2.
- l. Not required for the additional 4500 participants included in protocol amendments 2 and 3 to enlarge the size of the pediatric safety database or for participants under 5 years of age at enrollment.
- m. Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- n. Refer to [Section 8.3.1](#) for the time period for collecting SAEs.
- o. Following planned unblinding, any participant originally assigned to placebo who/whose parent/legal guardian declines the opportunity to receive BNT162b2 as part of the study, and the participant has therefore not received any active vaccine, should be withdrawn from the study. Those participants (or participants' parents/legal guardians) who decline the opportunity for the participant to receive a third dose of BNT162b2 as part of the study may be withdrawn from the study once the participant has reached 6 months after Dose 2.

1.3.2.1. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received BNT162b2 (≥6 Months to <12 Years Old Enrolled Before Protocol Amendment 6)

At the 6-month follow-up visit, all participants will be unblinded. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to their local or national recommendations prior to the 6-month follow-up visit (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo will have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of vaccination prior to the 6-month follow-up visit. After unblinding at the 6-month follow-up visit, participants who originally received BNT162b2 will follow this SoA for their remaining visits, after completing the SoA in [Section 1.3.2](#).

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that potential COVID-19/MIS-C symptoms are reported.

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received BNT162b2 (≥6 Months to <12 Years Old Enrolled Before Protocol Amendment 6)			
Visit Number	Visit X	Visit Y	Unplanned
Visit Description	Dose 3 6-Month Follow-up Visit	Dose 3 12-Month Follow-up Visit ^a	Potential COVID-19 Illness/MIS-C Visit ^{a,b}
Visit Window (Days)	175 to 189 Days After Visit 4A (≥6 M to <5 Y) OR Visit 5A (≥5 to <12 Y)	350 to 378 Days After Visit 4A (≥6 M to <5 Y) OR Visit 5A (≥5 to <12 Y)	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic or Telephone ^c	Clinic or Telephone	Clinic or Telehealth
For participants who are HIV positive, record latest CD4 count and HIV viral load	X	X	
Collect nonstudy vaccine information	X		
Collect prohibited medication use	X	X	X
Obtain anterior nasal swab			X
Collect blood sample for immunogenicity ^d	~5 mL	~5 mL	
Collect AEs as appropriate ^e	X	X	X
Collect SAEs as appropriate ^f	X		X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application		X ^g	
Collection of COVID-19/MIS-C-related clinical and laboratory information (including local diagnosis)			X

Abbreviations: CRF = case report form; HIV = human immunodeficiency virus; M = month(s); MIS-C = multisystem inflammatory syndrome in children; SMS = short message service; Y = year(s).

- This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point or prior to potential COVID-19 illness onset.
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.
- The participants who are part of the evaluation of persistence of immune response will have blood drawn either at Visit X or Visit Y. Note: This blood sample will not be required for participants as of October 2022.
- Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Refer to [Section 8.3.1](#) for the time period for collecting SAEs.
- When protocol amendment 8 is approved and participants are informed of early study completion, the e-diary device return should be arranged by the site.

1.3.2.2. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <12 Years Old Crossed Over Before Protocol Amendment 6)

At the 6-month follow-up visit, all participants will be unblinded at the time of this visit. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to the 6-month follow-up visit (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo, will have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of vaccination prior to the 6-month follow-up visit. When contacted, the site will conduct a telephone visit to confirm eligibility and, if the participant is eligible and wants to receive BNT162b2 in the event that he or she originally received placebo, the site will unblind the participant's study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2 (10 µg or 3 µg), the participant will move to the SoA immediately below (Section 1.3.2.2) for his or her remaining visits. Participants who originally received BNT162b2 will move to the SoA in [Section 1.3.2.1](#).

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that potential COVID-19/MIS-C symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness rather than vaccine reactogenicity. For details, see [Section 8.13](#).

Participants ≥6 months to <5 years old who originally received placebo and who enrolled before protocol amendment 6 but did not cross over (from placebo to active) before protocol amendment 6 should move to the SoA in [Section 1.3.2.3](#) following planned unblinding as per the SoA in [Section 1.3.2](#).

Participants enrolled in the ≥2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥5 to <12 years age group (ie, third dose administered at least 6 months after the second dose).

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <12 Years Old Enrolled & Crossed Over Before Protocol Amendment 6)								
Visit Number	A	B	C	D	E	F	G	Unplanned
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5 ^a	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit	Dose 5 12-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A	28 to 35 Days After Visit B	≥5 to <12 Y: At Least 175 Days After Visit B OR ≥6 M to <5 Y: At Least 60 Days After Visit B	28 to 35 Days After Visit D	175 to 189 Days After Visit D	350 to 378 Days After Visit D	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Telephone ^e	Clinic	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Obtain informed consent and assent (if appropriate)				X				
Confirm participant meets local/national recommending criteria or is at least 175 days after Dose 2 (Visit 2)	X							
Confirm participant originally received placebo	X							
For participants who are HIV positive, record latest CD4 count and HIV viral load	X		X	X	X	X	X	
Confirm use of contraceptives (if appropriate)	X	X	X	X	X			

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <12 Years Old Enrolled & Crossed Over Before Protocol Amendment 6)								
Visit Number	A	B	C	D	E	F	G	Unplanned
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5 ^a	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit	Dose 5 12-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A	28 to 35 Days After Visit B	≥5 to <12 Y: At Least 175 Days After Visit B OR ≥6 M to <5 Y: At Least 60 Days After Visit B	28 to 35 Days After Visit D	175 to 189 Days After Visit D	350 to 378 Days After Visit D	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Telephone ^e	Clinic	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Collect nonstudy vaccine information	X	X	X	X	X	X		
Collect prohibited medication use	X	X	X	X	X	X	X	X
Review and consider eligibility	X	X		X				
Review temporary delay criteria	X	X		X				
Measure vital signs (including body temperature)	X	X		X				
Perform physical examination ^f	X	X		X				
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X		X				

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <12 Years Old Enrolled & Crossed Over Before Protocol Amendment 6)								
Visit Number	A	B	C	D	E	F	G	Unplanned
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5 ^a	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit	Dose 5 12-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A	28 to 35 Days After Visit B	≥5 to <12 Y: At Least 175 Days After Visit B OR ≥6 M to <5 Y: At Least 60 Days After Visit B	28 to 35 Days After Visit D	175 to 189 Days After Visit D	350 to 378 Days After Visit D	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Telephone ^e	Clinic	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Obtain anterior nasal swab	X	X		X				X
Collect blood sample for immunogenicity	~5 mL ^g							
Obtain vaccine vial allocation via IRT	X							
Administer BNT162b2	X	X		X				
Assess acute reactions for at least 30 minutes after study intervention administration	X	X		X				
Collect AEs as appropriate ^h	X	X	X	X	X			X

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <12 Years Old Enrolled & Crossed Over Before Protocol Amendment 6)								
Visit Number	A	B	C	D	E	F	G	Unplanned
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5 ^a	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit	Dose 5 12-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A	28 to 35 Days After Visit B	≥5 to <12 Y: At Least 175 Days After Visit B OR ≥6 M to <5 Y: At Least 60 Days After Visit B	28 to 35 Days After Visit D	175 to 189 Days After Visit D	350 to 378 Days After Visit D	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Telephone ^e	Clinic	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Collect SAEs as appropriate ⁱ	X	X	X	X	X	X		X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application							X ^j	
Collection of COVID-19/MIS-C-related clinical and laboratory information (including local diagnosis)								X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; HIV = human immunodeficiency virus; IRT = interactive response technology; M = month(s); MIS-C = multisystem inflammatory syndrome in children; SMS = short message service; Y = year(s).

- In the US, the visit D Dose 5 will occur at least 140 days after visit B.
- This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point or prior to potential COVID-19 illness onset.
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <12 Years Old Enrolled & Crossed Over Before Protocol Amendment 6)								
Visit Number	A	B	C	D	E	F	G	Unplanned
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5 ^a	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit	Dose 5 12-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A	28 to 35 Days After Visit B	≥5 to <12 Y: At Least 175 Days After Visit B OR ≥6 M to <5 Y: At Least 60 Days After Visit B	28 to 35 Days After Visit D	175 to 189 Days After Visit D	350 to 378 Days After Visit D	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Telephone ^e	Clinic	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth

- f. A physical examination will include, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- g. Blood draw is only for participants who become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to Visit 5. Not required for the additional 4500 participants included to enlarge the size of the pediatric safety database in protocol amendments 2 (2250 ≥5- to <12-year-olds) and 3 (2250 <5-year-olds) or for participants under 5 years of age at enrollment.
- h. Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- i. Refer to [Section 8.3.1](#) for the time period for collecting SAEs.
- j. When protocol amendment 8 is approved and participants are informed of early study completion, the e-diary device return should be arranged by the site.

1.3.2.3. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)

At the 6-month follow-up visit, all participants will be unblinded at the time of this visit. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to 6 months after Dose 3 (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo, will have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of vaccination. When contacted, the site will conduct a telephone visit to confirm eligibility and, if the participant is eligible and wants to receive BNT162b2 in the event that he or she originally received placebo, the site will unblind the participant's study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2 (10 µg or 3 µg), the participant will move to the SoA immediately below (Section 1.3.2.3) for his or her remaining visits.

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that potential COVID-19/MIS-C symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness rather than vaccine reactogenicity. For details, see [Section 8.13](#).

Participants ≥6 months to <5 years old who originally received placebo enrolled and crossed over (from placebo to active vaccine) before protocol amendment 6 should move to the SoA in [Section 1.3.2.2](#) following planned unblinding as per the SoA in [Section 1.3.2](#).

Participants enrolled in the ≥2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥5 to <12 years age group (ie, third dose administered at least 6 months after the second dose).

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)								
Visit Number	A101	B102	C103	D104	E105	F106	G107	Unplanned
Visit Description	Dose 4	Dose 5	Dose 6 ^a	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit ^b	18-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d OR 175 to 189 Days After Visit 2 or Visit 403	19 to 23 Days After Visit A101	≥5 to <12 Y: At Least 175 Days After Visit B102 OR ≥6 M to <5 Y: 56 to 70 Days After Visit B102	28 to 35 Days After Visit C103	175 to 189 Days After C103	350 to 378 Days After C103	532 to 560 Days After C103	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Telephone	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Obtain informed consent and assent (if appropriate; if enrolled prior to protocol amendment 6 and crossed over after protocol amendment 6 – see Section 8.11.5.1)	X							
Confirm participant meets local/national recommending criteria or is 175 to 189 days after Visit 2 or Visit 403	X							

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)								
Visit Number	A101	B102	C103	D104	E105	F106	G107	Unplanned
Visit Description	Dose 4	Dose 5	Dose 6 ^a	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit ^b	18-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d OR 175 to 189 Days After Visit 2 or Visit 403	19 to 23 Days After Visit A101	≥5 to <12 Y: At Least 175 Days After Visit B102 OR ≥6 M to <5 Y: 56 to 70 Days After Visit B102	28 to 35 Days After Visit C103	175 to 189 Days After C103	350 to 378 Days After C103	532 to 560 Days After C103	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Telephone	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Confirm participant originally received placebo	X							
For participants who are HIV positive, record latest CD4 count and HIV viral load	X			X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X			
Collect prohibited medication use	X	X	X	X	X	X	X	X
Review and consider eligibility	X	X	X					
Review temporary delay criteria	X	X	X					
Measure vital signs (including body temperature)	X	X	X					

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)								
Visit Number	A101	B102	C103	D104	E105	F106	G107	Unplanned
Visit Description	Dose 4	Dose 5	Dose 6 ^a	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit ^b	18-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d OR 175 to 189 Days After Visit 2 or Visit 403	19 to 23 Days After Visit A101	≥5 to <12 Y: At Least 175 Days After Visit B102 OR ≥6 M to <5 Y: 56 to 70 Days After Visit B102	28 to 35 Days After Visit C103	175 to 189 Days After C103	350 to 378 Days After C103	532 to 560 Days After C103	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Telephone	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Perform clinical assessment ^e	X	X	X					
Obtain anterior nasal swab	X	X	X					X
Collect blood sample for immunogenicity	~5 mL ^f							
Obtain vaccine vial allocation via IRT	X							
Administer BNT162b2	X	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X	X					
Collect AEs as appropriate ^g	X	X	X	X				X

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)								
Visit Number	A101	B102	C103	D104	E105	F106	G107	Unplanned
Visit Description	Dose 4	Dose 5	Dose 6 ^a	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit ^b	18-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d OR 175 to 189 Days After Visit 2 or Visit 403	19 to 23 Days After Visit A101	≥5 to <12 Y: At Least 175 Days After Visit B102 OR ≥6 M to <5 Y: 56 to 70 Days After Visit B102	28 to 35 Days After Visit C103	175 to 189 Days After C103	350 to 378 Days After C103	532 to 560 Days After C103	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Telephone	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth
Collect SAEs as appropriate ^h	X	X	X	X	X			X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application							X ⁱ	
Collection of COVID-19/MIS-C-related clinical and laboratory information (including local diagnosis)								X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; HIV = human immunodeficiency virus; IRT = interactive response technology; MIS-C = multisystem inflammatory syndrome in children; SMS = short message service.

- In the US, the visit C103 Dose 6 will occur at least 140 days after visit B102.
- This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point or prior to potential COVID-19 illness onset.
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.

Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)								
Visit Number	A101	B102	C103	D104	E105	F106	G107	Unplanned
Visit Description	Dose 4	Dose 5	Dose 6 ^a	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit ^b	18-Month Follow-up Visit ^b	Potential COVID-19 Illness/MIS-C Visit ^{b,c}
Visit Window (Days)	From Recommendation ^d OR 175 to 189 Days After Visit 2 or Visit 403	19 to 23 Days After Visit A101	≥5 to <12 Y: At Least 175 Days After Visit B102 OR ≥6 M to <5 Y: 56 to 70 Days After Visit B102	28 to 35 Days After Visit C103	175 to 189 Days After C103	350 to 378 Days After C103	532 to 560 Days After C103	Optimally Within 3 Days After Potential COVID-19 Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Telephone	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth

- e. Including, if indicated, a physical examination.
- f. Blood draw is only required for participants enrolled after protocol amendment 6 (SoA in [Section 1.3.2.4](#), Visit 401 sequence). Blood draw is not required for those participants enrolled prior to protocol amendment 6 (SoA in [Section 1.3.2](#), Visit 1 sequence).
- g. Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- h. Refer to [Section 8.3.1](#) for the time period for collecting SAEs.
- i. When protocol amendment 8 is approved and participants are informed of early study completion, the e-diary device return should be arranged by the site.

1.3.2.4. Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that potential COVID-19/MIS-C symptoms are reported. During the 7 days following each dose, potential COVID-19/MIS-C symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19/MIS-C illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19/MIS-C illness rather than vaccine reactogenicity. For details, see [Section 8.13](#).

Administration of BNT162b2 to those originally assigned to placebo: At the time of the 6-month follow-up visit, all participants will be unblinded. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to 6 months after Dose 3 (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo, will have the opportunity to receive BNT162b2 (10 μg or 3 μg) based on age at the time of vaccination. When contacted, the site will conduct a telephone visit to confirm eligibility and, if the participant is eligible and wants to receive BNT162b2 in the event that he or she originally received placebo, the site will unblind the participant's study intervention allocation to determine whether the participant received BNT162b2 or placebo. In either scenario above, if he or she originally received placebo and wants to receive BNT162b2 (10 μg or 3 μg), the participant will move to the SoA in [Section 1.3.2.3](#) for his or her remaining visits. Participants who originally received BNT162b2 will complete the SoA immediately below (Section 1.3.2.4) before moving to the SoA in [Section 1.3.2.4.1](#).

Participants enrolled in the ≥ 2 to < 5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥ 5 to < 12 years age group (ie, third dose administered at least 5 months after the second dose).

Phase 2/3 Selected-Dose Portion: Participants ≥6 Months to <5 Years Old Enrolled From Protocol Amendment 6 Onwards						
Visit Number	401	402	403	404	405	Unplanned
Visit Description	Dose 1 ^a	Dose 2	Dose 3	1-Month Follow-up Visit	6-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 401	56 to 70 Days After Visit 402	28 to 35 Days After Visit 403	175 to 189 Days After Visit 403	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Obtain informed consent and assent (if appropriate)	X					
Assign participant number	X					
Obtain demography and significant medical history data (including breastfeeding) ^c	X	~ ^c	~ ^c	~ ^c	~ ^c	
For participants who are HIV positive, record latest CD4 count and HIV viral load	X			X	X	
Collect maternal COVID-19 immunization data for any COVID-19 vaccines given during pregnancy ^c	X	~ ^c	~ ^c	~ ^c	~ ^c	
Collect nonstudy vaccine information	X	X	X	X	X	
Collect prohibited medication use		X	X	X	X	X
Confirm eligibility	X	X	X			
Review temporary delay criteria	X	X	X			
Measure vital signs (including body temperature)	X	X	X			
Perform clinical assessment ^d	X	X	X			
Obtain randomization number and study intervention allocation	X					
Obtain anterior nasal swab	X	X	X			X

Phase 2/3 Selected-Dose Portion: Participants ≥6 Months to <5 Years Old Enrolled From Protocol Amendment 6 Onwards						
Visit Number	401	402	403	404	405	Unplanned
Visit Description	Dose 1 ^a	Dose 2	Dose 3	1-Month Follow-up Visit	6-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 401	56 to 70 Days After Visit 402	28 to 35 Days After Visit 403	175 to 189 Days After Visit 403	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Collect blood sample for immunogenicity	~5 mL			~5 mL ^c	~5 mL ^c	
Administer study intervention	X	X	X			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X	X			
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X					
Provide thermometer and caliper (measuring) device	X					
Reactivate reactogenicity e-diary		X	X			
Ensure the participant's parent(s)/legal guardian has a caliper device and thermometer		X	X			
Ask the participant's parent(s)/legal guardian to complete e-diary and ensure the participant's parent(s)/legal guardian remains comfortable with chosen e-diary platform	X	X	X			
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	↔	↔				

Phase 2/3 Selected-Dose Portion: Participants ≥6 Months to <5 Years Old Enrolled From Protocol Amendment 6 Onwards						
Visit Number	401	402	403	404	405	Unplanned
Visit Description	Dose 1 ^a	Dose 2	Dose 3	1-Month Follow-up Visit	6-Month Follow-up Visit	Potential COVID-19 Illness/MIS-C Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 401	56 to 70 Days After Visit 402	28 to 35 Days After Visit 403	175 to 189 Days After Visit 403	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone	Clinic or Telephone	Clinic or Telehealth
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X	X	X		
Collect AEs as appropriate ^f	X	X	X	X	X	X
Collect SAEs as appropriate ^g	X	X	X	X	X	X
Unblind the participant and move to either Section 1.3.2.4.1 or Section 1.3.2.3					X	
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)						X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; HIV = human immunodeficiency virus; MIS-C = multisystem inflammatory syndrome in children; SMS = short message service.

- This visit may be conducted across 2 consecutive dates; if so, please refer to [Section 8.11.2.1](#).
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- Collection of breastfeeding and maternal COVID-19 immunization data is only applicable to participants ≥6 months to <2 years of age. If not collected at an earlier visit, breastfeeding and maternal COVID-19 immunization data need to be collected (once only). Prior to collection of maternal COVID-19 vaccination data, the biological mother of the participant should sign the Release of Maternal COVID-19 Vaccination Information Form (see [Section 8.17](#)).
- Including, if indicated, a physical examination.
- The participants who are part of the immunogenicity subset will have blood drawn at Visit 404 and Visit 405. Note: For visit 405, this blood sample will not be required for participants as of October 2022.
- Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Refer to [Section 8.3.1](#) for the time period for collecting SAEs.

1.3.2.4.1. Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards Who Originally Received BNT162b2

After unblinding at the 6-month follow-up visit, or before if eligible per local or national recommendations, participants who originally received BNT162b2 will follow this SoA for their remaining visits, after completing the SoA in [Section 1.3.2.4](#).

An unplanned potential COVID-19/MIS-C illness visit is required at any time for the duration of the study that potential COVID-19/MIS-C symptoms are reported.

Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards Who Originally Received BNT162b2			
Visit Number	Visit X1	Visit Y1	Unplanned
Visit Description	Dose 3 12-Month Follow-up Visit ^a	Dose 3 18-Month Follow-up Visit ^a	Potential COVID-19 Illness/MIS-C Visit ^{a,b}
Visit Window (Days)	350 to 378 Days After Visit 403	532 to 560 Days After Visit 403	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic or Telephone ^c	Clinic or Telephone	Clinic or Telehealth
For participants who are HIV positive, record latest CD4 count and HIV viral load	X	X	
Collect prohibited medication use	X	X	X
Obtain anterior nasal swab			X
Collect blood sample for immunogenicity ^d	~5 mL	~5 mL	
Collect AEs as appropriate ^e	X	X	X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application		X ^f	

Phase 2/3 Selected-Dose Portion: Participants ≥6 Months to <5 Years Old Enrolled From Protocol Amendment 6 Onwards Who Originally Received BNT162b2			
Visit Number	Visit X1	Visit Y1	Unplanned
Visit Description	Dose 3 12-Month Follow-up Visit ^a	Dose 3 18-Month Follow-up Visit ^a	Potential COVID-19 Illness/MIS-C Visit ^{a,b}
Visit Window (Days)	350 to 378 Days After Visit 403	532 to 560 Days After Visit 403	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset
Type of Visit	Clinic or Telephone ^c	Clinic or Telephone	Clinic or Telehealth
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)			X

Abbreviations: CRF = case report form; HIV = human immunodeficiency virus; MIS-C = multisystem inflammatory syndrome in children; SMS = short message service.

- This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point or prior to potential COVID-19 illness onset.
- Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.
- The participants who are part of the immunogenicity subset will have blood drawn at either Visit X1 or Visit Y1. Note: This blood sample will not be required for participants as of October 2022.
- Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- When protocol amendment 8 is approved and participants are informed of early study completion, the e-diary device return should be arranged by the site.

1.3.3. Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing (≥ 5 to < 12 Years of Age, Placebo-Controlled, and ≥ 12 to < 16 Years of Age, Open-Label)

Administration of BNT162b2 to those originally assigned to placebo: At the 6-month follow-up visit, all participants will be unblinded (participants ≥ 5 to < 12 years of age only). Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to 6 months after Dose 2 (detailed separately and available in the electronic study reference portal) will be advised to contact the site to determine whether they can receive BNT162b2 (10 μg or 30 μg) based on age at the time of vaccination. When contacted, the site will conduct a telephone visit to confirm eligibility and, if the participant is eligible and wants to receive BNT162b2 in the event that he or she originally received placebo, the site will unblind the participant's study intervention allocation to determine whether the participant received BNT162b2 or placebo. If he or she originally received placebo and wants to receive BNT162b2 (10 μg or 30 μg), the participant will move to the SoA in [Section 1.3.3.1](#) for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

From protocol amendment 7, the SoAs include a third dose applicable to all enrolled participants. For all participants (≥ 5 to < 12 and ≥ 12 to < 16 years of age), the third dose will occur at least 5 months after Dose 2.

The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants ≥ 5 to < 12 years of age at the time of the second/third dose will receive the 10- μg dose level, and participants ≥ 12 years of age at the time of the second/third dose will receive the 30- μg dose level.

Participants ≥ 5 to < 12 years of age (placebo-controlled) who were enrolled and unblinded to study intervention allocation before protocol amendment 7 will proceed as follows:

- Participants who originally received BNT162b2 will receive the third dose at Visit 304A on this schedule.
- Participants who originally received placebo and crossed over to the SoA in [Section 1.3.3.1](#) will receive 3 doses of BNT162b2 at the appropriate dose interval as part of that schedule.
- Participants ≥ 12 to < 16 years of age (open-label) will receive the third dose of BNT162b2 at Visit 304A on this schedule.

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing (≥5 to <12 Years of Age, Placebo-Controlled, and ≥12 to <16 Years of Age, Open-Label)								
Visit Number	301	302	303	304	304A	304B	304C	305
Visit Description	Dose 1 ^a	Dose 2	4-Day Follow-up Visit	1-Month Follow-up Visit	Dose 3	Dose 3 4-Day Follow-up Visit	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 301	2 to 5 Days After Visit 302	28 to 35 Days After Visit 302	At Least 140 Days After Visit 302	2 to 5 Days After Visit 304A	28 to 35 Days After Visit 304A	175 to 189 Days After Visit 304A
Type of Visit	Clinic	Clinic	Clinic	Telephone ^b	Clinic	Clinic	Telephone	Clinic or Telephone
Obtain informed consent and assent (if appropriate)	X				X ^c			
Assign participant number	X							
Obtain demography and significant medical history data	X							
For participants who are HIV positive, record latest CD4 count and HIV viral load	X			X	X		X	X
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X			X			
Review temporary delay criteria	X	X			X			
Measure vital signs (including body temperature)	X	X			X			
Perform clinical assessment ^d	X	X			X			
Perform urine pregnancy test (only for female participants)	X	X			X			

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing (≥5 to <12 Years of Age, Placebo-Controlled, and ≥12 to <16 Years of Age, Open-Label)								
Visit Number	301	302	303	304	304A	304B	304C	305
Visit Description	Dose 1 ^a	Dose 2	4-Day Follow-up Visit	1-Month Follow-up Visit	Dose 3	Dose 3 4-Day Follow-up Visit	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 301	2 to 5 Days After Visit 302	28 to 35 Days After Visit 302	At Least 140 Days After Visit 302	2 to 5 Days After Visit 304A	28 to 35 Days After Visit 304A	175 to 189 Days After Visit 304A
Type of Visit	Clinic	Clinic	Clinic	Telephone ^b	Clinic	Clinic	Telephone	Clinic or Telephone
biologically capable of having children)								
Obtain randomization number and study intervention allocation	X							
Obtain anterior nasal swab	X	X			X			
Collect blood sample for potential troponin level testing	~5 mL		~5 mL			~5 mL		
Administer study intervention	X	X			X			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X			X			
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X				X			
Provide thermometer and caliper (measuring) device	X							
Reactivate reactivity e-diary		X			X			
Ensure the participant's parent(s)/legal guardian has a caliper device and thermometer		X			X			

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing (≥5 to <12 Years of Age, Placebo-Controlled, and ≥12 to <16 Years of Age, Open-Label)								
Visit Number	301	302	303	304	304A	304B	304C	305
Visit Description	Dose 1 ^a	Dose 2	4-Day Follow-up Visit	1-Month Follow-up Visit	Dose 3	Dose 3 4-Day Follow-up Visit	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 301	2 to 5 Days After Visit 302	28 to 35 Days After Visit 302	At Least 140 Days After Visit 302	2 to 5 Days After Visit 304A	28 to 35 Days After Visit 304A	175 to 189 Days After Visit 304A
Type of Visit	Clinic	Clinic	Clinic	Telephone ^b	Clinic	Clinic	Telephone	Clinic or Telephone
Ask the participant's parent(s)/legal guardian to complete e-diary and ensure the participant's parent(s)/legal guardian remains comfortable with chosen e-diary platform	X	X			X			
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	↔				↔			
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X			X	
Collect AEs as appropriate ^e	X	X	X	X	X	X	X	
Collect SAEs as appropriate ^f	X	X	X	X	X	X	X	X
Unblind the participant and move to either Section 1.3.3.1 or continue on this SoA as appropriate ^g								X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application								X ⁱ

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing (≥5 to <12 Years of Age, Placebo-Controlled, and ≥12 to <16 Years of Age, Open-Label)								
Visit Number	301	302	303	304	304A	304B	304C	305
Visit Description	Dose 1 ^a	Dose 2	4-Day Follow-up Visit	1-Month Follow-up Visit	Dose 3	Dose 3 4-Day Follow-up Visit	Dose 3 1-Month Follow-up Visit	Dose 3 6-Month Follow-up Visit ^b
Visit Window (Days)	Day 1	19 to 23 Days After Visit 301	2 to 5 Days After Visit 302	28 to 35 Days After Visit 302	At Least 140 Days After Visit 302	2 to 5 Days After Visit 304A	28 to 35 Days After Visit 304A	175 to 189 Days After Visit 304A
Type of Visit	Clinic	Clinic	Clinic	Telephone ^b	Clinic	Clinic	Telephone	Clinic or Telephone

Abbreviations: AESI = adverse event of special interest; HIV = human immunodeficiency virus; SMS = short message service; SoA = schedule of activities.

- This visit may be conducted across 2 consecutive dates; if so, please refer to [Section 8.11.8.1](#).
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.
- Only applicable to participants enrolled before protocol amendment 7.
- Including, if indicated, a physical examination.
- Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)).
- Refer to [Section 8.3.1](#) for the time period for collecting SAEs.
- This is applicable to the ≥5- to <12-year-old age group (placebo-controlled).

1.3.3.1. Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing: Participants Who Originally Received Placebo (≥5 to <12 Years of Age)

After unblinding at the 6-month follow-up visit, or before if eligible per local or national recommendations, participants who originally received placebo will follow this SoA for their remaining visits.

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing: Participants Who Originally Received Placebo (≥5 to <12 Years of Age)						
Visit Number	A1	B1	C1	D1	E1	F1
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit
Visit Window (Days)	From Recommendation ^a or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A1	28 to 35 Days After Visit B1	At Least 140 Days After Visit B1	28 to 35 Days After Visit D1	175 to 189 Days After Visit D1
Type of Visit	Clinic	Clinic	Telephone ^b	Clinic	Telephone	Clinic or Telephone
Obtain informed consent and assent (if appropriate)				X		
Confirm participant meets local/national recommending criteria or is at least 175 days after Dose 2 (Visit 302)	X					
Confirm participant originally received placebo	X					
For participants who are HIV positive, record latest CD4 count and HIV viral load	X		X	X	X	X
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X	X
Collect prohibited medication use	X	X	X	X	X	X
Review and consider eligibility	X	X		X		

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing: Participants Who Originally Received Placebo (≥5 to <12 Years of Age)						
Visit Number	A1	B1	C1	D1	E1	F1
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit
Visit Window (Days)	From Recommendation ^a or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A1	28 to 35 Days After Visit B1	At Least 140 Days After Visit B1	28 to 35 Days After Visit D1	175 to 189 Days After Visit D1
Type of Visit	Clinic	Clinic	Telephone ^b	Clinic	Telephone	Clinic or Telephone
Review temporary delay criteria	X	X		X		
Measure vital signs (including body temperature)	X	X		X		
Perform clinical assessment ^c	X	X		X		
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X		X		
Obtain anterior nasal swab	X	X		X		
Collect blood sample for potential troponin level testing	~5 mL ^d					
Obtain vaccine vial allocation via IRT	X					
Administer BNT162b2	X	X		X		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X		X		
Collect AEs as appropriate ^e	X	X	X	X	X	
Collect SAEs as appropriate ^f	X	X	X	X	X	X

Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing: Participants Who Originally Received Placebo (≥5 to <12 Years of Age)						
Visit Number	A1	B1	C1	D1	E1	F1
Visit Description	Dose 3	Dose 4	1-Month Follow-up Visit	Dose 5	Dose 5 1-Month Follow-up Visit	Dose 5 6-Month Follow-up Visit
Visit Window (Days)	From Recommendation ^a or 175 to 189 Days After Dose 2	19 to 23 Days After Visit A1	28 to 35 Days After Visit B1	At Least 140 Days After Visit B1	28 to 35 Days After Visit D1	175 to 189 Days After Visit D1
Type of Visit	Clinic	Clinic	Telephone ^b	Clinic	Telephone	Clinic or Telephone
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application						X

Abbreviations: AESI = adverse event of special interest; HIV = human immunodeficiency virus; IRT = interactive response technology; SMS = short message service.

- For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
- Contact can be made via email or SMS. If no response is obtained or responses do not satisfy visit requirements, a telephone call should be made.
- Including, if indicated, a physical examination.
- Blood draw is only for participants who become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to Visit 303.
- Refer to [Section 8.3.1](#) for the time period for collecting AEs/AESIs. Any AEs occurring up to 48 hours after blood draw and anterior nasal swab collection must be recorded (see [Section 8.3.1](#)).
- Refer to [Section 8.3.1](#) for the time period for collecting SAEs.

2. INTRODUCTION

The BNT162b2 RNA-based COVID-19 vaccine is being investigated for prevention of COVID-19 in healthy children.

2.1. Study Rationale

The purpose of the dose-finding/selected-dose study is to rapidly describe the safety, tolerability, immunogenicity, and efficacy (depending on accrual of sufficient cases) of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy children. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or development of COVID-19 in participants under 16 years of age. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).¹ Elevated troponin I level may be an indicator of subclinical myocarditis. If testing of troponin I levels in individuals who did not receive BNT162b2 indicates that troponin I level could be a reliable indicator of potential subclinical myocarditis, obtaining serum samples for potential troponin I testing in an additional group of participants during the period of increased risk of clinical myocarditis may help characterize the absence/presence and frequency of subclinical myocarditis.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the WHO and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to SARS virus isolates than to another coronavirus infecting humans, the MERS virus.^{2,3}

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of infections in countries worldwide. Children have been affected by both the primary COVID-19 disease and the less common secondary inflammatory complications, including MIS-C.^{4,5}

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.⁶ The WHO Weekly Epidemiology Update Report dated 27 September 2020 noted more than 32.7 million COVID-19 cases and 991,000 deaths globally, including 16,233,110 confirmed cases with 546,864 deaths in the Americas.⁷ COVID-19 is generally milder in children than adults, possibly because common risk factors for severe COVID-19 in adults are generally less prevalent in pediatric age groups. Children present with fever and dry cough over half the time and symptoms can include GI symptoms, including diarrhea and vomiting, and in some cases can be the only presenting features. Pulmonary involvement in symptomatic children is generally mild.^{8,9,10} Nevertheless, severe cases, including those requiring intensive care support, have been reported.⁴ Of US children diagnosed with COVID-19, 5.7% to 20% were hospitalized, including 0.58% to 2.0% admitted to an ICU.¹¹

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.^{5,12} MIS-C is a febrile hyperinflammatory condition with frequent evidence of cardiac damage and dermatologic, mucocutaneous, and GI features.¹² The syndrome appears to have some overlap with Kawasaki disease shock syndrome.^{13,14} 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.¹⁵ As of 29 June 2020, approximately 1000 cases have been reported.¹⁵ 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%).¹⁶ Death rates of 2% to 4% have been reported.¹⁵ MIS-C has been reported in many countries throughout North America, Europe, Asia, and Latin America,¹⁷ including the US,^{5,12} Italy,¹⁸ and France.¹⁹ The United States currently has the most reported cases globally, with the number of confirmed cases continuing to rise globally. BNT162b2 was approved by the FDA on 23 August 2021 to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.^{20,21}

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.^{20,21}

A Phase 1/2/3 study (C4591001) is being conducted in healthy individuals 12 years of age and older to investigate the safety, tolerability, immunogenicity, and efficacy of the prophylactic BNT162 vaccine candidates against COVID-19. The vaccine candidate selected for evaluation in the C4591001 Phase 2/3 study is BNT162b2 at a dose level of 30 µg and as 2 doses given approximately 21 days apart. On 18 November 2020, the primary efficacy analysis results were announced, which demonstrated BNT162b2 to be 95% effective against COVID-19 beginning 7 days after the second dose; 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group. Safety data from approximately 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 µg in participants 16 years of age and older.²² 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.²³ On 10 May 2021, the US FDA issued an EUA for use in individuals 12 through 15 years of age. Other countries have also granted EUA or other authorization/approval for this age group (eg, EMA, UK, Switzerland, and the Philippines).

This Phase 1/2/3 study (C4591007) will initially evaluate up to 3 different dose levels of BNT162b2 in up to 3 age groups (participants ≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years of age). Safety, tolerability, immunogenicity, and efficacy (depending on successful immunobridging and accrual of a sufficient number of cases) will be evaluated. Phase 1 includes the dose-finding portion. Initiation of dose finding in participants ≥ 5 to <12 years of age will be based on the acceptable blinded safety data demonstrated in 2260 12- through 15-year-olds at the 30-µg dose level in the C4591001 study.²⁴ The Phase 2/3 BNT162b2 dose level to be used in each age group in this study will be selected based on the Phase 1 safety, tolerability, and immunogenicity data from the same age group. Phase 2/3 (referred to as the selected-dose portion of the study) includes an immunobridging analysis of immune responses in participants ≥ 6 months to <12 years of age to those in participants 16 to 25 years of age in the Phase 3 C4591001 efficacy study. Safety, tolerability, and efficacy (depending on successful immunobridging and accrual of a sufficient number of cases) will also be evaluated in Phase 2/3 of this study.

Immunobridging criteria comparing participants ≥ 6 months to <2 years of age (3-µg dose) to participants 16 to 25 years of age were met both for the GMR and for seroresponse; however, these criteria were not met for participants ≥ 2 to <5 years of age. Given the emerging data in individuals 16 years of age and older that a third dose may extend high levels of protection, including against the Omicron variant, a third dose may optimally protect individuals ≥ 6 months to <2 years of age and 2 to <5 years of age from COVID-19. Although the study remains blinded, ongoing safety assessments in these 2 age groups continue to show a favorable safety profile.²⁵ In addition, a third dose at least 6 months after the second dose will also be incorporated for participants who are ≥ 5 to <12 years of age. The authorized dose of BNT162b2 in adolescents and young adults 12 years and older is 30 µg, whereas in the Phase 2/3 portion of the ongoing C4591007 study the following doses were selected: 10 µg in participants ≥ 5 to <12 years of age and 3 µg in participants ≥ 6 months to <5 years of

age. The Phase 2/3 BNT162b2 dose schedule will be selected based on the Phase 1 assessments. The Phase 2/3 part will assess immunobridging of immune responses in participants within each age group to participants in the 30-µg Phase 3 C4591001 efficacy study.

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).¹ Elevated troponin I level may be an indicator of subclinical myocarditis. If testing of troponin I levels in individuals who did not receive BNT162b2 indicates that troponin I level could be a reliable indicator of potential subclinical myocarditis, obtaining serum samples for potential troponin I testing in an additional group of participants during the period of increased risk of clinical myocarditis may help characterize the absence/presence and frequency of subclinical myocarditis.

On 29 October 2021, the US FDA issued an EUA for use in individuals ≥ 5 to <12 years of age.²⁶ Enrollment by ≥ 5 to <12 -year-olds was completed at the time of this EUA. Age-eligible participants were unblinded and if administered placebo were offered active immunization. Other countries have also granted authorization/approval for this age group (eg, EMA, Canada, and New Zealand),^{27,28,29} and Pfizer and BioNTech are anticipating further regulatory decisions in other countries. On 17 May 2022, the US FDA expanded the EUA authorizing a booster dose for administration to individuals >5 to <12 years of age at least 5 months after completion of a primary series of BNT162b2.³⁰ On 17 June 2022, the US FDA issued the EUA authorizing primary series of 3 doses of BNT162b2 in children 6 months through 4 years of age, in which the initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.³¹ Per the protocol, age-eligible participants were unblinded and if they received placebo were offered active immunization. Approximately 5800 total participants 6 months to <5 years were enrolled (~3600 total participants 2 to <5 years; ~2200 total participants 6 months to <2 years) by August 2022 when the enrollment stopped. A recommendation issued by the FDA on 30 Jun 2022 described the need to modify existing vaccines to address circulating variants and requested that manufacturers begin clinical trials with modified vaccines containing an Omicron BA.4/BA.5 component. On 12 October 2022, the US FDA amended the EUA authorizing bivalent BNT162b2 (original/Omi BA.4/BA.5) for use as a single booster dose for the ≥ 5 to <12 years age group for administration at least 2 months following completion of the primary or booster vaccination.³² Additionally, on 08 December 2022, the US FDA issued the EUA authorizing bivalent BNT162b2 (original/Omi BA.4/BA.5) for use as a third dose of the 3-dose primary series for individuals 6 months through 4 years of age (3-µg dose level).³³

On 14 March 2023 the US FDA amended the EUA of bivalent BNT162b2 (Original/Omi BA.4/BA.5) to provide for a single booster dose in children 6 months through 4 years of age at least 2 months after completion of the primary vaccination with 3 doses of monovalent BNT162b2.³⁴

Since the initiation of this study, many protocol amendments have been implemented in order to adapt to expanding knowledge about COVID-19, the emergence of variants, and growing knowledge about duration of vaccine effectiveness. These amendments have included unblinding and vaccination of initial placebo recipients and administration of booster doses, to ensure that participants have been protected in line with national and local guidelines as they have been determined. Therefore, the study is now fully unblinded with no control arm, making it observational in nature, and the active safety surveillance for most participants has been completed. Real-world studies of both safety and effectiveness of BNT162b2 have contributed enormously, and continue to do so, to the knowledge about the vaccine beyond what is possible within the clinical trial setting. In view of this, protocol amendment 8 will truncate participants' study involvement to allow early completion of the study without the need to complete all study visits as per the SoA. Following the appropriate approvals of protocol amendment 8, participants will be informed via the study sites that their participation in the study will be concluded early with no further data collection required 6 months after the third dose of BNT162b2.

Protocol amendment 8 will also remove the objective to evaluate the immunogenicity and safety of lower dose levels of BNT162b2 in individuals 12 through <30 years of age. In November 2022, the US FDA concluded that the lower-dose evaluation substudy is no longer warranted, taking into consideration the safety surveillance data on the postmarketing use of COMIRNATY® and the Pfizer-BioNTech COVID-19 vaccine as well as the ongoing postmarketing safety surveillance activities, including those designed to evaluate known risks of myocarditis and pericarditis.

2.2.1. Clinical Overview

The BNT162 vaccine candidates use an RNA to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect. This vaccine is for the prevention of COVID-19. Prior to this study, clinical data from the BNT162b2 vaccine established a favorable safety profile, with mild, localized, and transient effects. The C4591001 study³⁵ is currently in Phase 3, which includes >40,000 individuals in the US and other countries, of whom >21,000 participants have now been administered BNT162b2 at the 30-µg dose level on a 2-dose schedule.³⁶ Vaccine-related enhanced disease for vaccines against related coronaviruses (SARS-CoV-1 and MERS) has been reported only in animal models.^{37,38} To date, no enhanced disease has been observed in SARS-CoV-2 animal models with any SARS-CoV-2 vaccine platform, including RNA-based vaccines. Such effects have not been documented so far for SARS-CoV-2. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no approved or licensed preventive options available. However, based on the data available from the C4591001 study, multiple temporary or emergency use authorizations have been granted. The available safety and immunogenicity data from the ongoing Pfizer/BioNTech clinical trial combined with available nonclinical data with BNT162 vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable benefit/risk profile and support continued clinical development of BNT162b2.

In the C4591001 study, BNT162b2 has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. 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%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of participants reporting hypersensitivity-related AEs was numerically higher in the active vaccine group compared with the placebo group (137 [0.63%] vs 111 [0.51%]). Severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) (<2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited AEs, lymphadenopathy occurred much more frequently in the active vaccine group than the placebo group and is plausibly related to vaccination. SAEs, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study.²²

The safety and immunogenicity of a third dose of BNT162b2 30 µg were studied in 306 people 18 through 55 years of age a median of 6.8 months after their second dose; these data demonstrated a strong immune response. The geometric mean neutralizing antibody titers against the reference strain were approximately 3-fold higher 1 month after the third dose compared to 1 month after Dose 2.³⁹ The following risk (more frequent than listed above) has been determined to be caused by BNT162b2 following an additional third dose: common (between 1 in 10 and 1 in 100 people): enlarged lymph glands. It was also determined that following a third dose of BNT162b2, the following risks were not reported: hives, itching, lethargy, sweating and night sweats, feeling weak or unwell, and swelling of the face or lips.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. The 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. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of VAED. Continued clinical investigation is justified given the:

- Urgent need for the development of a more stable prophylactic vaccine for COVID-19;

- Threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection;
- Potential of the BioNTech platform of RNA-based vaccines to rapidly deliver high numbers of vaccine doses in a single production campaign.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 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]		
Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain, fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines as well as the COVID-19 vaccine.	<ul style="list-style-type: none"> The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. All study participants will be observed for at least 30 minutes after vaccination.
<p>The safety profile of a novel vaccine is not yet fully characterized.</p> <p>Adverse reactions (risks) identified from the postauthorization safety data include: Anaphylaxis, other hypersensitivity reactions (eg, rash, pruritus, urticaria, angioedema), and pain in extremity (injected arm).</p>	<p>Data available from the C4591001 study showed low incidence of severe or serious events, and no clinically concerning safety observations across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.</p> <p>Postauthorization safety data surveillance has confirmed the safety profile observed in the C4591001 study and has resulted in identification of some additional adverse reactions (risks) as noted in this table.</p>	<ul style="list-style-type: none"> AE and SAE reports will be collected from the signing of the ICD to 1 month after the second dose of vaccine. DMC will review all safety data throughout the study. All participants will be observed for at least 30 minutes after vaccination.
Unknown AEs with a novel vaccine in children <12 years of age.	Data available from the C4591001 study showed low incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well-tolerated across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.	The current Phase 3 C4591001 study includes participants 12 years of age and older.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
A theoretical risk of vaccination with BNT162b2 or BNT162b2 OMI is VAED or VAERD.	Disease enhancement has been seen following RSV, feline coronavirus, and dengue virus vaccinations. It is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection. No evidence of disease enhancement has been seen in a large-scale clinical study of BNT162b2 in humans or in postauthorization surveillance.	Monitoring for cases of COVID-19 developing during the study, which will be reported at COVID-19 illness visits. Assessments of individual cases for disease enhancement is challenging based on the current understanding of the mechanism of pathogenesis, thus evaluations of any adverse or unexpected imbalances in severe COVID-19 cases may provide insight on a potential signal for this theoretical risk.
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.
Very rare cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.	Anaphylaxis: Frequency not known. 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 8.14 .

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/MIS-C illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant's parent(s)/legal guardian performing an anterior nasal swab for 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 draw.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially 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 taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162b2 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

The dose-finding/selected-dose age groups referred to in the objectives and estimands below are participants ≥ 5 to < 12 years, ≥ 2 to < 5 years, and ≥ 6 months to < 2 years of age.

The obtaining-serum-samples-for-potential-troponin I-testing age groups referred to in the objectives and estimands below are a separate cohort of participants ≥ 5 to < 12 years and ≥ 12 to < 16 years.

3.1. Phase 1

Phase 1		
Objectives	Estimands	Endpoints
Primary:	Primary:	Primary:
To describe the safety and tolerability profiles of prophylactic BNT162b2 at each dose level in each age group.	<p>In participants receiving at least 1 dose of study intervention, the percentage of participants in each age group reporting:</p> <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from Dose 1 to 1 month after Dose 2 SAEs from Dose 1 to 6 months after Dose 2 AEs from Dose 3 to 1 month after Dose 3 SAEs from Dose 3 to 6 months after Dose 3 	<p>Participants ≥ 5 to <12, and ≥ 2 to <5 years of age:</p> <ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs <p>Participants ≥ 6 months to <2 years of age:</p> <ul style="list-style-type: none"> Local reactions (tenderness at the injection site, redness, and swelling) Systemic events (fever, decreased appetite, drowsiness, and irritability) AEs SAEs
Secondary:	Secondary:	Secondary:
To describe the immune responses elicited by prophylactic BNT162b2 at each dose level in each age group.	<p>In participants complying with the key protocol criteria (evaluable participants) in each age group:</p> <ul style="list-style-type: none"> GMTs at each time point 	<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers
Exploratory:	Exploratory:	Exploratory:
To describe COVID-19 and severe COVID-19 cases with and without serological or virological evidence of past SARS-CoV-2 infection.		<ul style="list-style-type: none"> Confirmed COVID-19 cases Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection.		<ul style="list-style-type: none"> Confirmed cases as per CDC criteria

3.2. Phase 2/3

Phase 2/3		
Objectives	Estimands	Endpoints
Primary Safety:	Primary Safety:	Primary Safety:
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> (selected-dose and obtaining-serum-samples-for-potential-troponin I-testing portions of the study) in Phase 2/3 in each age group.	In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants in each age group reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from Dose 1 to 1 month after Dose 2 SAEs from Dose 1 to 6 months after Dose 2 AEs from Dose 3 to 1 month after Dose 3 SAEs from Dose 3 to 6 months after Dose 3 	Participants ≥ 12 to <16 , ≥ 5 to <12 , and ≥ 2 to <5 years of age: <ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs Participants ≥ 6 months to <2 years of age: <ul style="list-style-type: none"> Local reactions (tenderness at the injection site, redness, and swelling) Systemic events (fever, decreased appetite, drowsiness, and irritability) AEs SAEs
Primary Immunogenicity (Selected-Dose 2-Dose Series):	Primary Immunogenicity (Selected-Dose 2-Dose Series):	Primary Immunogenicity (Selected-Dose 2-Dose Series):
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in each age group and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:	<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers
<ul style="list-style-type: none"> In participants ≥ 5 to <12 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. 	<ul style="list-style-type: none"> GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants ≥ 5 to <12 years of age to those in participants 16-25 years of age 1 month after Dose 2 from Phase 2/3 of the C4591001 study The difference in percentages of participants with seroresponse^a in participants ≥ 5 to <12 years of age and participants 16 to 25 years of age from Phase 2/3 of the C4591001 study 	

Phase 2/3		
Objectives	Estimands	Endpoints
<ul style="list-style-type: none"> In participants ≥ 2 to < 5 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. 	<ul style="list-style-type: none"> GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants ≥ 2 to < 5 years of age to those in participants 16 to 25 years of age 1 month after Dose 2 from Phase 2/3 of the C4591001 study The difference in percentages of participants with seroresponse in participants ≥ 2 to < 5 years of age and participants 16 to 25 years of age from Phase 2/3 of the C4591001 study 	
<ul style="list-style-type: none"> In participants ≥ 6 months to < 2 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. 	<ul style="list-style-type: none"> GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants ≥ 6 months to < 2 years of age to those in participants 16 to 25 years of age 1 month after Dose 2 from Phase 2/3 of the C4591001 study The difference in percentages of participants with seroresponse in participants ≥ 6 months to < 2 years of age and participants 16 to 25 years of age from Phase 2/3 of the C4591001 	
Primary Immunogenicity (Selected-Dose 3-Dose Series):	Primary Immunogenicity (Selected-Dose 3-Dose Series):	Primary Immunogenicity (Selected-Dose 3-Dose Series):
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in each age group and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 3) of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection:	<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers

Phase 2/3		
Objectives	Estimands	Endpoints
<ul style="list-style-type: none"> In participants ≥ 2 to < 5 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. 	<ul style="list-style-type: none"> GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 in participants ≥ 2 to < 5 years of age to those at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study The difference in percentages of participants with seroresponse at 1 month after Dose 3 in participants ≥ 2 to < 5 years of age and at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study 	
<ul style="list-style-type: none"> In participants ≥ 6 months to < 2 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. 	<ul style="list-style-type: none"> GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 in participants ≥ 6 months to < 2 years of age to those at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study The difference in percentages of participants with seroresponse at 1 month after Dose 3 in participants ≥ 6 months to < 2 years of age and at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study 	
Secondary Immunogenicity/Efficacy:	Secondary Immunogenicity/Efficacy:	Secondary Immunogenicity/Efficacy:
To describe the immune responses elicited by prophylactic BNT162b2 at the dose level selected in each age group in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection.	In evaluable participants with no serological or virological evidence of past SARS-CoV-2 infection from each vaccine and age group: <ul style="list-style-type: none"> GMTs at each time point GMFRs from before Dose 1 to each subsequent time point after Dose 2 or Dose 3 	<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers

Phase 2/3		
Objectives	Estimands	Endpoints
Secondary Efficacy (Selected-Dose 2-Dose Series):	Secondary Efficacy (Selected-Dose 2-Dose Series):	Secondary Efficacy (Selected-Dose 2-Dose Series):
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 to prior to Dose 3 during the blinded follow-up period in participants in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection:	<ul style="list-style-type: none"> Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up
<ul style="list-style-type: none"> In the ≥ 5 to <12 years age group in the selected-dose portion of the study, if immunobridging is successful and if at least 21 cases are accrued. 	<ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo] 	
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 to prior to Dose 3 during the blinded follow-up period in participants in the selected-dose portion of the study with or without evidence of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection:	<ul style="list-style-type: none"> Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up
<ul style="list-style-type: none"> In ≥ 5 to <12 years age group in the selected-dose portion of the study, if immunobridging is successful and if at least 21 cases are accrued. 	<ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo] 	
Secondary Efficacy (Selected-Dose 3-Dose Series):	Secondary Efficacy (Selected-Dose 3-Dose Series):	Secondary Efficacy (Selected-Dose 3-Dose Series):
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥ 6 months to <5 years of age in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection.	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection: <ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo] 	<ul style="list-style-type: none"> Confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up

Phase 2/3		
Objectives	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥ 6 months to < 5 years of age in the selected-dose portion of the study with or without evidence of past SARS-CoV-2 infection.	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection: <ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo] 	<ul style="list-style-type: none"> Confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up
Exploratory:	Exploratory:	Exploratory:
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 to prior to Dose 3 through the blinded follow-up period in participants in the selected-dose portion of the study without, and with and without, evidence of past SARS-CoV-2 infection in each age group and in ≥ 6 months to < 2 years and ≥ 2 to < 5 years age groups combined.	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: <ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo] 	<ul style="list-style-type: none"> COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥ 6 months to < 5 years of age in the selected-dose portion of the study without, and with and without, evidence of past SARS-CoV-2 infection in each age group.	In participants complying with the key protocol criteria (evaluable participants) after receipt of the third dose of study intervention: <ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo] 	<ul style="list-style-type: none"> COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT

Phase 2/3		
Objectives	Estimands	Endpoints
To describe the relative VE of prophylactic BNT162b2 against confirmed COVID-19 illness from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 during the same calendar time interval of interest. Participants from the original active vaccine group receiving 3 doses of BNT162b2 will be compared to participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding in each age group and the ≥ 6 -month to <2-year and ≥ 2 - to <5-year age groups combined.	In all participants from the original active vaccine group receiving 3 doses of BNT162b2 and participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding: <ul style="list-style-type: none"> $100 \times (1 - \text{IRR})$ [ratio of original active vaccine to placebo crossover] 	<ul style="list-style-type: none"> COVID-19 incidence per 1000 person-years based on central laboratory or locally confirmed NAAT
To evaluate the immune response elicited by prophylactic BNT162b2 at the dose level selected in each age group in Phase 2/3 participants with and without serological or virological evidence of past SARS-CoV-2 infection.	In evaluable participants with or without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: <ul style="list-style-type: none"> GMCs and/or GMTs at each time point GMFRs from before Dose 1 to each subsequent time point after Dose 2 or Dose 3 	<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers
To describe severe COVID-19 cases in participants in the selected-dose portion of the study with and without serological or virological evidence of past SARS-CoV-2 infection.		<ul style="list-style-type: none"> Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection in participants in the selected-dose portion of the study.		<ul style="list-style-type: none"> Confirmed cases as per CDC criteria
To describe the safety and immunogenicity of prophylactic BNT162b2 at the dose level selected in each age group in children with stable HIV disease.		<ul style="list-style-type: none"> All safety and immunogenicity endpoints described above will be analyzed descriptively
To describe the immune response to emerging VOCs.		<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers for VOCs

Phase 2/3		
Objectives	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain in a subset of participants.		
To describe the frequency of elevated troponin I levels at baseline and after Vaccination 2 and/or 3 if testing is indicated based upon data accrued outside of this study.		
To describe the SARS-CoV-2 lineage distribution among participants as determined by next-generation sequencing.		
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	<ul style="list-style-type: none"> COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

- a. Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times$ LLOQ is considered seroresponse.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2/3 study in healthy children and young adults.

Dependent upon safety and/or immunogenicity data generated during the course of this study, and the resulting assessment of benefit-risk, the safety, tolerability, and immunogenicity of BNT162b2 in participants <6 months of age may subsequently be evaluated. Participants will range from ≥ 6 months to <16 years of age with different dose levels assessed in each group.

Table 1. Dose Levels for Each Age Group in the Phase 1 and Phase 2/3 Dose-Finding/Selected-Dose Evaluations, and Obtaining Serum Samples for Potential Troponin I Testing

Phase 1 Open-Label Dose-Finding Evaluation ^a					
	≥ 6 Months to <2 Years	≥ 2 to <5 Years	≥ 5 to <12 Years	≥ 12 to <16 Years	Total
Dose level	3 μ g	3/10 μ g	10/20/30 μ g		
Participants	16 ^b	16/32 ^b	16/16/16 ^c		112
Phase 2/3 Observer-Blinded, Placebo-Controlled Selected-Dose Evaluation ^a					
Dose level	3 μ g	3 μ g	10 μ g	30 μ g	

Table 1. Dose Levels for Each Age Group in the Phase 1 and Phase 2/3 Dose-Finding/Selected-Dose Evaluations, and Obtaining Serum Samples for Potential Troponin I Testing

Participants (Planned Enrollment)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	Any participants who turn 12 during the course of the study will be offered the 30-µg dose level for all subsequent doses	13,500
	≥6 Months to <2 Years	≥2 to <5 Years	≥5 to <12 Years	≥12 to <16 Years	Total
Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing					
Planned dose level			10 µg	30 µg	
Participants (Planned Enrollment)			750 (active 500; placebo 250)	500 (active 500; placebo 0)	1250
Phase 2/3 total by age group (Planned Enrollment)	4500 (active 3000; placebo 1500)	4500 (active 3000; placebo 1500)	5250 (active 3500; placebo 1750)	500 (active 500; placebo 0)	14,750

- The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination.
- Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
- Actual number of participants recruited in the ≥5 to <12 years age group. Dose 1: 16 out of 16 received 30-µg dose level; Dose 2: 4 out of 16 received 30-µg dose level and 12 of 16 received 10-µg dose level.

4.1.1. Phase 1

Dose-finding: Is the open-label dose-finding portion of the study that will evaluate safety, tolerability, and immunogenicity of BNT162b2 administered on a 2-dose (separated by approximately 21 days) schedule in up to 3 age groups (participants ≥5 to <12 years, ≥2 to <5 years, and ≥6 months to <2 years of age).

Dose finding is being initiated in this study in participants ≥5 to <12 years of age based on the acceptable blinded safety assessment of the 30-µg dose in 12- to 15-year-olds in the C4591001 study.

The purpose of Phase 1 is to identify preferred dose level(s) of BNT162b2 from up to 3 different dose levels in each age group.

Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose.

Update as part of protocol amendment 6: All participants will receive a third dose of BNT162b2. For participants ≥ 6 months to < 5 years of age, the third dose will occur at least 8 weeks after the second dose. In participants ≥ 5 to < 12 years of age, the third dose will occur at least 6 months after the second dose (updated to at least 5 months for US participants as part of protocol amendment 8). The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the third dose of BNT162b2 will be based on age at the time of vaccination: participants < 5 years of age at the time of the third dose will receive the 3- μ g dose level, participants ≥ 5 to < 12 years of age at the time of the third dose will receive the 10- μ g dose level, and participants ≥ 12 years of age at the time of the third dose will receive the 30- μ g dose level.

Participants will have blood drawn prior to both Dose 1 and Dose 2 and 7 days after Dose 2 to assess for immunogenicity to determine the final BNT162b2 dose level for Phase 2/3. Participants will also have blood drawn prior to Dose 3 and 1, 6, and 12 months after Dose 3 (As of 01 September 2022, a blood sample will not be required at 1, 6, and 12 months after Dose 3).

4.1.2. Phase 2/3

Selected-dose: Is the portion of the study that will evaluate safety, tolerability, and immunogenicity in each age group at the selected dose level from the Phase 1 dose-finding portion of the study. Efficacy will be evaluated within or across age groups in which immunobridging is successful, depending on accrual of a sufficient number of cases in those age groups.

Participants will have blood drawn at baseline prior to Dose 1 (for all participants) and 6 months after Dose 2 (for participants ≥ 5 to < 12 years of age only, not in safety expansion). Immunobridging to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at (1) baseline and 1 month after Dose 2 and (2) baseline and 1 month after Dose 3. The persistence of the immune response will be based on immunogenicity data collected in participants at (1) baseline and 1 and 6 months after Dose 2 and (2) baseline and 1, 6, 12, and 18 months after Dose 3 (As of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8). In addition, efficacy against confirmed COVID-19 infection will also be assessed.

At designated US sites, an additional optional whole blood sample of approximately 10 mL will be obtained prior to Dose 1 and at 7 days and 6 months after Dose 2 from up to approximately 60 participants ≥ 10 years of age. Additional samples will be obtained prior to Dose 3 and 1 month after Dose 3 (original BNT162b2 group only). These samples will be used on an exploratory basis to investigate the postvaccination cell-mediated immune response at these time points.

At the 6-month follow-up visit, all participants will be unblinded. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another

COVID-19 vaccine according to local or national recommendations prior to the 6-month follow-up visit (Visit 5 or 405) (detailed separately and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo, will have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of the vaccination prior to the 6-month follow-up visit (Visit 5 or Visit 405).

Update as part of protocol amendment 6: All participants will receive a third dose of BNT162b2. For participants ≥ 6 months to < 5 years of age, the third dose will occur at least 8 weeks after the second dose. In participants ≥ 5 to < 12 years of age, the third dose will occur at least 6 months after the second dose (updated to at least 5 months for US participants as part of protocol amendment 8). The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants < 5 years of age at the time of the second/third dose will receive the 3-µg dose level, participants ≥ 5 to < 12 years of age at the time of the second/third dose will receive the 10-µg dose level, and participants ≥ 12 years of age at the time of the second/third dose will receive the 30-µg dose level.

Participants enrolled in the ≥ 2 to < 5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥ 5 to < 12 years age group (ie, third dose administered at least 6 months after the second dose, updated to at least 5 months for US participants as part of protocol amendment 8).

Obtaining serum samples for potential troponin I testing: If testing of troponin I levels in individuals who did not receive BNT162b2 indicates that troponin I level could be a reliable indicator of potential subclinical myocarditis, obtaining serum samples for potential troponin I testing during the period of increased risk of clinical myocarditis may help characterize the absence/presence and frequency of subclinical myocarditis. To assess, an additional group of participants will be included: ≥ 5 to < 12 years: randomized 2:1 to receive BNT162b2 10 µg or placebo, and ≥ 12 to < 16 years of age: open-label receipt of BNT162b2 30 µg.

Update as part of protocol amendment 7: All participants will receive a third dose of BNT162b2. For all participants (≥ 5 to < 12 and ≥ 12 to < 16 years of age), the third dose will occur at least 5 months after Dose 2.

The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants ≥ 5 to < 12 years of age at the time of the second/third dose will receive the 10-µg dose level, and participants ≥ 12 years of age at the time of the second/third dose will receive the 30-µg dose level.

Protocol amendment 8 will truncate participants' study involvement to allow early completion of the study without the need to complete all study visits as per the SoA.

4.1.3. Number of Participants

4.1.3.1. Phase 1: Open-Label Dose-Finding

Phase 1 is an open-label study that will consist of up to 3 different dose levels in each age group, with a minimum of 16 participants per dose level (total of 144 participants) for the dose-finding evaluation; see Table 2.

Table 2. Phase 1 Dose-Finding Participants

Age Group	Total	Up to 3 Dose Levels of BNT162b2 ^a	Active	Placebo
≥5 to <12 Years	48	16/16/16	16	N/A
≥2 to <5 Years	48	16/16/16	16	N/A
≥6 Months to <2 years	48	16/16/16	16	N/A

a. A dose level may be expanded to enroll more than 16 participants per dose level.

4.1.3.2. Phase 2/3: Safety, Tolerability, Immunogenicity, and Efficacy

Selected-dose: Is the portion of the study that will evaluate the safety, tolerability, and immunogenicity of the selected dose level in each age group at the selected dose level from Phase 1 dose finding, with a total of approximately 13,500 participants as an additional 4500 participants will be included to further enlarge the size of the pediatric safety database. Participants will be randomized in a 2:1 ratio to receive active vaccine or placebo (Table 3 and Table 4).

Approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) randomized in each age group in this phase will contribute to the immunobridging analysis at 1 month after Dose 2 and 100 participants in the active vaccine group will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2 and 6, 12, and 18 months after Dose 3 (as of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8). These participants will be enrolled from across study sites to ensure this subset is representative of the whole study.

Approximately 250 participants (200 in the active vaccine group and 50 in the placebo group) randomized in each younger age group (≥6 months to <2 years and ≥2 to <5 years of age) in this phase will contribute to the immunobridging analysis at 1 month after Dose 3 (participants who are currently enrolled prior to protocol amendment 6).

For the persistence time points of 6 and 12 months after Dose 3, approximately 100 participants from each age group enrolled prior to protocol amendment 6 in the original BNT162b2 group will have an immunogenicity blood draw in order to contribute to the analysis (as of 20 October 2022, a blood sample is no longer required at 6 and 12 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8).

All approximately 13,500 participants will contribute to the VE analysis. Efficacy will be evaluated for ≥ 5 to < 12 years and the combination of ≥ 6 months to < 2 years and ≥ 2 to < 5 years of age if immunobridging is successful, depending on accrual of a sufficient number of cases in those age groups.

At designated US sites, an additional optional whole blood sample of approximately 10 mL will be obtained prior to Dose 1 and at 7 days and 6 months after Dose 2 from up to approximately 60 participants ≥ 10 years of age. Additional samples will be obtained prior to Dose 3 and 1 month after Dose 3 (original BNT162b2 group only). These samples will be used on an exploratory basis to investigate the postvaccination cell-mediated immune response at these time points.

Table 3. Phase 2/3 Selected-Dose Participants Enrolled Before Protocol Amendment 6 – Blood Draws for Immunogenicity/Efficacy Assessments

	All Age Groups			≥ 5 to < 12 Years of Age			≥ 2 to < 5 Years and ≥ 6 Months to < 2 Years of Age ^a		
	Total	Active	Placebo	Total	Active	Placebo	Total	Active	Placebo
Baseline blood draw (Visit 1)	9000	6000	3000	4500	3000	1500	2250	1500	750
1 Month after Dose 2 (Visit 4)	1350	900	450	450	300	150	450	300	150
6 Months after Dose 2 (Visit 5)	Up to 2250	Up to 1500	Up to 750	Up to 2250	Up to 1500	Up to 750	N/A	N/A	N/A
Dose 3	7500	6000	Up to 1500	3000	3000	N/A	2250	1500	Up to 750
1 Month after Dose 3	7500	6000	Up to 1500	3000	3000	N/A	2250	1500	Up to 750
6 Months after Dose 3 ^b	300	300	N/A	100	100	N/A	100	100	N/A
12 Months after Dose 3 ^b	300	300	N/A	100	100	N/A	100	100	N/A

Note: Because of operational considerations, the numbers in these age groups may vary.

- Number of participants shown is for each of these 2 younger age groups.
- This assessment is not required as of 20 October 2022..

Enrolled from protocol amendment 6 onwards: Among participants ≥ 6 months to < 2 years and ≥ 2 to < 5 years of age enrolled after protocol amendment 6, approximately 300 participants (200 in the active vaccine group and 100 in the placebo group) randomized in each age group will have an immunogenicity blood draw at 1 month after Dose 3 and approximately 100 participants in the original BNT162b2 group will have an immunogenicity blood draw at 6, 12, and 18 months after Dose 3 (as of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3).

Table 4. Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards (3-Dose Series) – Blood Draws for Immunogenicity/Efficacy Assessments

	All Age Groups			≥ 6 Months to < 2 Years of Age			≥ 2 to < 5 Years of Age		
	Total	Active	Placebo	Total	Active	Placebo	Total	Active	Placebo
Baseline blood draw	4500	3000	1500	2250	1500	750	2250	1500	750
1 Month after Dose 3 ^a	600	400	200	300	200	100	300	200	100
6 Months after Dose 3 ^b	200	200	N/A	100	100	N/A	100	100	N/A
12 Months after Dose 3 ^b	200	200	N/A	100	100	N/A	100	100	N/A
18 Months after Dose 3 ^b	200	200	N/A	100	100	N/A	100	100	N/A

Note: Because of operational considerations, the numbers in these age groups may vary.

- Unblinding had been initiated based on the EUA for the primary series received on 17 June 2022 for ages 6 months to < 5 years resulting in placebo participants being unblinded. No further blood draws for this group will be required.
- These assessments are no longer required as of 20 October 2022.

All participants will contribute to the safety, tolerability, and efficacy assessments (Table 5).

Table 5. Phase 2/3 Selected-Dose Participants – Safety and Tolerability/Efficacy Assessments

Age	Total	Active	Placebo
≥ 5 to < 12 Years	4500	3000	1500
≥ 2 to < 5 Years	4500	3000	1500
≥ 6 Months to < 2 Years	4500	3000	1500
All age groups (Planned Enrollment)	13,500	9000	4500

On 29 October 2021, the US FDA issued an EUA for use in individuals ≥ 5 to <12 years of age. Enrollment by ≥ 5 to <12 -year-olds was completed at the time of this EUA. On 17 June 2022, the US FDA issued the EUA for a primary series of 3 doses of BNT162b2 in children 6 months through 4 years of age, in which the initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose. Per the protocol, age-eligible participants were unblinded and if they received placebo were offered active immunization. Approximately 5800 total participants 6 months to <5 years were enrolled (~3600 total participants 2 to <5 years; ~2200 total participants 6 months to <2 years) by August 2022 when the enrollment stopped.

Obtaining serum samples for potential troponin I testing: 750 participants ≥ 5 to <12 years of age (randomized 2:1 to receive BNT162b2 10 μg or placebo) and 500 participants ≥ 12 to <16 years of age (open-label receipt of BNT162b2 30 μg) (Table 6).

Table 6. Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing – Blood Draws for Potential Troponin I Level Evaluation

	Sum of Age Groups Currently Included in Potential Troponin I Testing Within Protocol			≥ 5 to <12 Years of Age Placebo-Controlled (2:1 Randomization)			≥ 12 to <16 Years of Age Open-Label		
	Total	Active	Placebo	Total	Active	Placebo	Total	Active	Placebo
Baseline blood draw	1250	1000	250	750	500	250	500	500	N/A
4 Days after Dose 2	1250	1000	250	750	500	250	500	500	N/A
4 Days after Dose 3	1250	1250	N/A	750	750	N/A	500	500	N/A

4.1.4. Intervention Groups and Duration

Phase 1 open-label dose-finding: Dosing will begin at the low-dose level in participants ≥ 5 to <12 years of age. Controlled enrollment will be required for the first dose level studied in each age group. Only a limited number of participants (~4) are dosed before allowing dosing in the remaining participants (~12) in the same age and dose-level group. The IRC will review safety data (e-diary and AE) acquired up to 7 days after Dose 1 for the low-dose level group; upon confirmation of an acceptable safety assessment by the IRC:

- Dosing may commence at the mid-dose level in the same age group, and
- Dosing may commence at the low-dose level in participants ≥ 2 to <5 years of age.

The same process will be followed when moving up dose levels in each age group, and when progressing between age groups at the low-dose level as shown in [Section 1.2](#). Dosing may commence at the low-dose level in participants ≥ 6 months to < 2 years of age after IRC review of safety data (e-diary and AE) acquired up to 7 days after Dose 1 at the low-dose level from participants ≥ 2 to < 5 years of age.

In each age group, if the low-dose level is considered not acceptable based on safety assessment after Dose 1, the mid-dose level or high-dose level will not commence. In this case, an optional lower dose level may commence. Dependent on the results obtained, dose level(s) may be omitted. In each age group, if the mid-dose level is considered not acceptable based on safety assessment after Dose 1, the high-dose level will not commence.

Based on safety assessment, the second dose may be given at a lower dose level.

Duration of the dose-finding portion of the study: Participants are expected to participate for approximately 19 months.

Phase 2/3 selected-dose: Progression of each age group into Phase 2/3 will occur independently; it is therefore possible that each age group may not start Phase 2/3 concurrently and the dose level selected for Phase 2/3 may differ in each age group. For each age group to proceed to Phase 2/3, safety, tolerability, and immunogenicity data from 7 days after Dose 2 for the selected vaccine dose level in the age group from Phase 1 will be confirmed to be acceptable.

Duration of the selected-dose portion of the study:

Protocol amendment 8 will truncate participants' study involvement to allow early completion of the study without the need to complete all study visits as per the SoA.

- Participants ≥ 6 months to < 12 years old enrolled before protocol amendment 6 who originally received BNT162b2 are expected to participate for approximately 19 months.
- Participants ≥ 6 months to < 12 years old that cross over (from placebo to active) before protocol amendment 6 who originally received placebo are expected to participate for approximately 25 months.
- Participants ≥ 6 months to < 5 years old enrolled from protocol amendment 6 onwards who originally received BNT162b2 are expected to participate for approximately 21 months.
- Participants ≥ 6 months to < 5 years old that cross over (from placebo to active) after protocol amendment 6 who originally received placebo are expected to participate for approximately 21 months.

Obtaining serum samples for potential troponin I testing: Progression of each age group will occur concurrently.

Duration of obtaining serum samples for potential troponin I testing: Participants are expected to participate for up to a maximum of approximately 13 months.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19/MIS-C in Phase 1 dose-finding and Phase 2/3 selected-dose participants will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in [Section 8.13](#), a COVID-19/MIS-C illness visit will occur and an anterior nasal swab) will be taken for antigen assessment as well as recording of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis). For participants in the troponin group, COVID-19/MIS-C will be reported as AESIs.

Human reproductive safety data are not available for BNT162b2 RNA-based COVID-19 vaccine, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see [Appendix 4](#)) for WOCBP.

4.3. Justification for Dose

Dose-finding and selected-dose evaluation: Based on acceptable blinded safety data in 2260 12- through 15-year-olds at the 30-μg dose level in the C4591001 study, dose-finding is considered in this study using the same vaccine candidate.²⁴ Therefore, this study will start with a 10-μg dose level for Phase 1 participants ≥5 to <12 years of age, which was well tolerated in adults 18 to 55 years of age in C4591001, before moving to another dose level in this age group or initiating the younger age groups (20 μg, 30 μg with an option of 3 μg).

Update as part of protocol amendment 6: All participants will receive a third dose of BNT162b2. Immunobridging criteria comparing participants ≥6 months to <2 years of age (3-μg dose) to participants 16 to 25 years of age were met both for the GMR and for seroresponse; however, these criteria were not met for participants 2 to <5 years of age. Given the emerging data in individuals 16 years of age and older that a third dose may extend high levels of protection, including against the Omicron variant, a third dose may optimally protect individuals ≥6 months to <2 years of age and ≥2 to <5 years of age from COVID-19. Ongoing safety assessments in these 2 age groups continue to show a favorable safety profile.²⁵ In addition, a third dose at least 6 months after the second dose will also be incorporated for participants who are ≥5 to <12 years of age.

The interval between the second and third doses will be based on the participant's age at the time of enrollment. The dose level of the second and third doses of BNT162b2 will be based on age at the time of vaccination: participants <5 years of age at the time of the second/third dose will receive the 3-μg dose level, participants ≥5 to <12 years of age at the time of the second/third dose will receive the 10-μg dose level, and participants ≥12 years of age at the time of the second/third dose will receive the 30-μg dose level.

Obtaining serum samples for potential troponin I testing (≥5 to <12 years of age, placebo-controlled, and ≥12 to <16 years of age, open-label): The authorized dose of BNT162b2 in adolescents and young adults 12 years of age and older is 30 μg, whereas in the ongoing C4591007 Phase 2/3 portion of the study, 10 μg in participants ≥5 to <12 years was selected.

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 prescriber 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.

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 between ≥6 months and <12 years of age, at the time of randomization, at Visit 1 for the dose-finding/selected-dose evaluation.

For the **obtaining-serum-samples-for-potential-troponin I-testing portion of the study:**

- Male or female participants between ≥5 and <16 years of age.

- Refer to Appendix 4 for reproductive criteria for male ([Section 10.4.1](#)) and female ([Section 10.4.2](#)) participants.

Type of Participant and Disease Characteristics:

2. Participants' parent(s)/legal guardian(s) and participants, 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. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in the therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

Phase 2/3: Specific criteria for such participants with known stable infection with HIV, HCV, or HBV can be found in [Section 10.7](#).

4. Participants are expected to be available for the duration of the study and whose parent(s)/legal guardian can be contacted by telephone during study participation.
5. Negative urine pregnancy test for female participants who are biologically capable of having children.
6. 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.

Informed Consent:

7. The participant or participant's parent(s)/legal guardian is capable of giving signed informed consent as described in [Appendix 1](#), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).

The investigator, or a person designated by the investigator, will obtain written or electronically signed informed consent (and assent) from each study participant or participant's legal guardian (as defined in [Appendix 1](#)) and the participant's assent, when applicable, before any study-specific activity is performed. All 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/assent document.

5.2. Exclusion Criteria

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

Medical Conditions:

1. **Phase 1 only:** 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.
2. **Phase 1 only:** Known infection with HIV, HCV, or HBV.
3. Receipt of medications intended to prevent COVID-19.
4. Previous or current diagnosis of MIS-C.
5. 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. Note: This includes both conditions that may increase the risk associated with study intervention administration or a condition that may interfere with the interpretation of study results
6. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
7. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
8. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus. Note: Stable type 1 diabetes and hypothyroidism are permitted.
9. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
10. Female who is pregnant or breastfeeding.

Prior/Concomitant Therapy:

11. Previous vaccination with any coronavirus vaccine.
12. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
13. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration, or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

14. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.
15. Previous participation in other studies involving study intervention containing LNPs.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

16. 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.

5.3. Lifestyle Considerations

5.3.1. Contraception

All male and female participants who, in the opinion of the investigator, are biologically capable of having children must agree to use a highly effective method of contraception consistently and correctly for at least 28 days after the last study vaccination.

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 4, [Section 10.4.4](#)) 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). In addition, the investigator or designee will instruct the participant or participant's parent(s)/legal guardian as applicable 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 randomly assigned to study intervention/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/Study Intervention Administration

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 $\geq 100.4^{\circ}\text{F}$ [$\geq 38^{\circ}\text{C}$]) or other acute illness within 48 hours before study intervention administration. This includes a positive SARS-CoV-2 test (rapid antigen or NAAT) within 28 days. For Phase 1, confirmed COVID-19 diagnosis is an exclusion criterion.
2. Receipt of any nonlive vaccine, any seasonal or pandemic influenza vaccine, or any rotavirus vaccine within 14 days before study intervention administration, or any other live vaccine (ie, excluding live influenza and rotavirus vaccines) within 28 days before study intervention administration.
3. Anticipated receipt of any nonlive vaccine, any seasonal or pandemic influenza vaccine, or any rotavirus vaccine within 14 days or any other live vaccine within 28 days after study intervention administration.
4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

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. In Phase 2/3, the selected-dose and obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years old) portions are placebo-controlled and the obtaining-serum-samples-for-potential-troponin I-testing (≥ 12 to < 16 years old) portion is open-label.

The Phase 1 dose-finding portion will evaluate a 2-dose (separated by approximately 21 days) schedule of up to 3 different dose levels of RNA vaccine candidate BNT162b2 for active immunization against COVID-19, to determine the final dose level of BNT162b2 in the selected-dose portion of Phase 2/3 for each age group. The investigational RNA vaccine candidate and saline placebo, in Phase 2/3 of the selected-dose and obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years old) portions, are the 2 potential study interventions that may be administered to a study participant:

- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): 10 μg , 20 μg , and 30 μg , with an option for 3 μg or another dose level.
- Normal saline (0.9% sodium chloride solution for injection).

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)	Saline Placebo (Selected-Dose and Obtaining-Serum- Samples-for-Potential- Troponin I-Testing Portions [≥ 5 to < 12 Years Old])
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 $\mu\text{g}/0.5\text{ mL}$	100 $\mu\text{g}/\text{mL}$, 0.4-mL vial	N/A
Dosage Level(s) ^a	10 μg , 20 μg , or 30 μg , with an option for 3 μg or another dose level	3 μg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor

Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)	Saline Placebo (Selected-Dose and Obtaining-Serum- Samples-for-Potential- Troponin I-Testing Portions [≥ 5 to < 12 Years Old])
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.	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement.	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement.

- a. Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose.

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit in accordance with the study's [SoA](#). The volume to be administered may vary by dose level; full details are described in the IP manual.

For participants ≥ 2 years of age, study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. Study intervention will be administered by an **unblinded** administrator.

For participants < 2 years of age, study intervention should be administered intramuscularly into the anterior thigh muscle, preferably of the left leg. Study intervention will be administered by an **unblinded** administrator.

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, 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/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions 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 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 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.
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.
9. 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 an appropriately 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.

Study intervention and placebo (for the Phase 2/3 selected-dose and obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years) portions of the study) will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way as to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

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

6.3.2. Blinding of Site Personnel (Phase 2/3 Selected-Dose Portion and Obtaining-Serum-Samples-for-Potential-Troponin I-Testing Portion [≥ 5 to < 12 Years Old] Only)

The study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because BNT162b2 and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

At the 6-month follow-up visit, all participants will be unblinded. Participants who originally received placebo will be offered the opportunity to receive BNT162b2 as part of the study. If participants in any country become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to the 6-month follow-up visit (detailed separately, and available in the electronic study reference portal), then all participants in the study, regardless of their country of residence, who originally received placebo, will have the opportunity to receive BNT162b2 (10 μ g or 3 μ g) based on

age at the time of vaccination. At the time of protocol amendment 8, the study is fully unblinded with no control arm.

For the participants in the Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing portion of the study (≥ 12 to < 16 years), in which only active vaccine is being administered, blinding is not applicable. The majority of sponsor staff will be blinded to study intervention allocation in the Phase 2/3 selected-dose and Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years) portions of the study. All laboratory personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study in the Phase 2/3 selected-dose portion of the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in the Phase 2/3 selected-dose portion of the study (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s) who are not direct members of the study team and will not participate in any other study-related activities will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see [Section 9.6](#)). This will comprise a statistician and programmer(s).
- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. With the exception of a small group of statisticians and programmers, who will become unblinded at the participant level at the time of the first planned reporting event for the Phase 2/3 selected-dose portion of the study for a given age group to perform the analyses, other members of this team will only be unblinded at the group level and not have access to individual participant assignments. A separate group of statisticians and programmers will remain blinded and continue supporting the blinded conduct of the study.
- At Visit 5, Visit 405, Visit 305, or other time during the Phase 2/3 selected-dose and obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years) portions of the study, when a participant who originally received placebo receives BNT162b2 per the SoAs in [Section 1.3.2.2](#), [Section 1.3.2.3](#), and [Section 1.3.3.1](#) or becomes eligible for receipt of BNT162b2 according to recommendations, the study team will become unblinded to the participant's original study intervention allocation.
- After the study data used for submission become public, the blinded study team will also have access to those data and become unblinded at a group level.

6.3.4. Breaking the Blind

For the Phase 2/3 selected-dose and obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years) portions of the study up to the 6-month follow-up visit, the IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

Instructions on how to unblind participants at the 6-month follow-up visit will be provided separately. Note: The Impala (randomization and drug management system) IRT Break Blind function must ONLY be used for emergency break blind and NOT for confirmation of receipt of placebo.

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, as well as the anatomical location, 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 identification 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. Concomitant Therapy

6.5.1. 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, with the exception of nonstudy COVID-19 vaccines (see [Section 7](#)).

- Medications or vaccinations should not be withheld if required for a participant's medical care.
- Receipt of any nonlive vaccine, any seasonal or pandemic influenza vaccine, or any rotavirus vaccine within 14 days, or any live vaccine (ie, excluding live influenza and rotavirus vaccines) within 28 days, before study intervention administration.

- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, is prohibited within 60 days before enrollment through conclusion of the study.
- Receipt of systemic corticosteroids (>2 mg/kg/dose of prednisone or equivalent) for ≥ 14 days is prohibited from 28 days prior to enrollment through the 1-month follow-up after Dose 3.
- Receipt of blood/plasma products, immunoglobulins, or monoclonal antibodies is prohibited within 60 days before enrollment through conclusion of the study.
- Receipt of any passive antibody therapy, including monoclonal antibodies, specific to COVID-19 is prohibited within 90 days before enrollment through conclusion of the study.
- 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.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

The use of topical anesthetics for blood draws is permitted.

Medication other than that described as prohibited in [Section 6.5.1](#) required for treatment of preexisting stable conditions is permitted.

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

6.5.3. Recording Nonstudy Vaccination and Concomitant Medications

The following nonstudy vaccinations (to include start date) and concomitant medications (to include start and stop dates and name of the medication) will be recorded in the CRF if administration occurred during study participation, unless otherwise noted:

- Details of any nonstudy vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 5 and Visit 5C for Phase 1 dose-finding participants and Visit 5 and Visit X for Phase 2/3 selected-dose participants who originally received BNT162b2; Visit 305 for Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing participants; Visit F and Visit 105 for Phase 2/3 selected-dose participants who originally received placebo; and Visit F1 for Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years old) participants who originally received placebo only; Visit 405 for Phase 2/3 selected-dose participants ≥ 6 months to < 5 years of age enrolled from protocol amendment 6 onwards; Visit E105 for Phase 2/3 selected-dose participants ≥ 6 months to < 5 years of age enrolled from protocol amendment 6 onwards who originally received placebo).
- Prohibited medications (not intended to treat COVID-19/MIS-C illness) listed in [Section 6.5.1](#) of the protocol will be recorded in the prohibited medication CRF.
- Prohibited COVID-19 vaccinations listed in [Section 6.5.1](#) will be recorded in the concomitant vaccination CRF.
- Any prescribed medication to treat or intended to treat COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.
- Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose level from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, because of a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.7](#).

- Discuss contraceptive use as described in [Section 5.3.1](#).
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention intramuscularly:
 - For participants ≥ 2 years of age: should be administered into the deltoid muscle, preferably of the nondominant arm.
 - For participants < 2 years of age, should be administered into the anterior thigh muscle, preferably of the left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- The participant or participant's parent(s)/legal guardian as applicable should continue to adhere to the participant's current visit schedule, but the participant must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited by unscheduled telephone contact(s) and/or in-person visit(s).

6.6. Intervention After the End of the Study

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

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 may include the following: AEs, participant 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 the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered.

Note: Phase 1 participants with a positive SARS-CoV-2 NAAT result without symptoms do not meet exclusion criterion 1 and this should not result in discontinuation of study intervention. However, a confirmed COVID-19 diagnosis with the presence of at least 1 of the symptoms meets exclusion criterion 1 and the participant should be discontinued from study intervention (see [Section 8.16](#)).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, tolerability, immunogenicity, and efficacy. 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 the request of the participant or his or her parent(s) and/or legal guardian. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant/participant's parent(s)/legal guardian request;
- Investigator request;
- Protocol deviation.

From protocol amendment 5 onwards, participants who receive COVID-19 vaccines outside of the study should be withdrawn. This does not apply if the nonstudy COVID-19 vaccine was administered prior to site receipt of IRB/EC approval of protocol amendment 5.

Following planned unblinding, as per the [SoA](#) for each portion of the study, any participant originally assigned to placebo who/whose parent/legal guardian declines the opportunity for the participant to receive BNT162b2 as part of the study, and the participant has therefore not received any active vaccine, should be withdrawn from the study.

Those participants who/whose participants' parent/legal guardians decline the opportunity for the participant to receive a third dose of BNT162b2 as part of the study should be withdrawn from the study once they have reached 6 months after Dose 2.

If a participant does not return for a scheduled visit, every effort should be made to contact him or her or the participant's parent(s)/legal guardian as applicable. 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 participant or participant's parent(s)/legal guardian should be questioned regarding the reason for the participant's withdrawal. 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, the participant or 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 participant's parent(s)/legal guardian or a child who has provided assent during any phase of the study withdraws from the study and also withdraws consent/assent (Section 7.2.1) for disclosure of further 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

A participant who has provided assent during any phase of the study, or a participant's parent(s)/legal guardian who requests to discontinue receipt of study intervention, will remain in the study, and the participant 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 persons previously authorized to provide this information. The participant or participant's parent(s)/legal guardian 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 the participant or participant's parent(s)/legal guardian is unable to be contacted by the study site.

The following actions must be taken if a participant or participant's parent(s)/legal guardian fails to attend a required study visit:

The site must attempt to contact the participant or participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible and counsel the participant or participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant or participant's parent(s)/legal guardian wishes for the participant 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 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 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 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 individual participants <12 years of age in this study is approximately 25 mL for Phase 1 and Phase 2/3 participants who will contribute to immunogenicity assessments (excluding obtaining-serum-samples-for-potential-troponin I-testing participants). The remaining Phase 2/3 participants will have a total blood sampling volume of 20 mL. Those participants in the subset who consent to additional blood collection for isolation of PBMCs may have a total blood sampling volume up to approximately 70 mL. For participants in the obtaining-serum-samples-for-potential-troponin I-testing portion of the study, approximately 10 mL of blood will be collected.

8.1. Efficacy and/or Immunogenicity Assessments

Surveillance for potential cases of COVID-19 and MIS-C will occur throughout a participant's involvement in the study to describe both COVID-19 and MIS-C.

If, at any time, a participant in the Phase 1 dose-finding/Phase 2/3 selected-dose portions of the study develops an acute illness (described in [Section 8.13](#)), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.⁴⁰ In this circumstance, the participant's parent(s)/legal guardian should contact the site. An in-person or telehealth visit should occur, and assessments should be conducted as specified in the [SoA](#). The assessments will include a nasal (anterior nares) swab sample collection either by site staff personnel (clinical visit) or by a participant's parent/legal guardian, which will be tested at a central laboratory using an RT-PCR test (Cepheid; US 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 8.13](#)) 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)

Two definitions (first and second definitions) of SARS-CoV-2–related cases, SARS-CoV-2–related severe cases, and MIS-C will be considered in assessing COVID-19/MIS-C cases. In all cases, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness:

SARS-CoV-2–Related Cases

Confirmed COVID-19, first definition: 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), which triggers a potential COVID-19 illness visit (see [Section 8.13.1](#)):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea, as defined by ≥ 3 loose stools/day;
- Vomiting;
- Inability to eat/poor feeding in participants <5 years of age.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>), but does not trigger a potential COVID-19 illness visit unless in the opinion of the PI deemed necessary:

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea or abdominal pain¹¹;
- Lethargy.

COVID-19 Cases Without Coinfection of Other Pathogens

For participants <5 years of age, positive RT-PCR cases confirmed by the central laboratory or valid local test will undergo BioFire testing for coinfection with other pathogens. The confirmed COVID-19 cases without coinfection of any other pathogens will be considered as another supportive definition.

SARS-CoV-2–related severe case definition: Confirmed COVID-19 and presence of at least 1 of the following triggers a potential COVID-19 illness visit:

- Clinical signs at rest indicative of severe systemic illness (RR (breaths/min) and HR (beats/min) as shown in Table 7⁴¹; SpO₂ ≤92% on room air or >50% FiO₂ to maintain ≥92%, or PaO₂/FiO₂ <300 mm Hg);

Table 7. RR and HR, by Age, Indicative of Severe Systemic Illness

Participant Age	RR	HR
6 to <9 Months	>61	>168
9 Months to <12 months	>58	>161
12 to <18 Months	>53	>156
18 to <24 Months	>46	>149
2 to <3 Years	>38	>142
3 to <4 Years	>33	>136
4 to <6 Years	>29	>131
6 to <8 Years	>27	>123
8 to <12 Years	>25	>115

Abbreviations: HR = heart rate; RR = respiratory rate.

Note: This table is based on data obtained from: 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.

Note: It is anticipated that HR and RR measurements would be obtained from medical records generated as part of the participant's standard of care. Efforts should be made to measure HR and RR when the participant is not crying or anxious, and measurements should be repeated as needed to ensure an accurate and reliable measurement. Only measurements considered clinically significant by the investigator should be reported in the CRF. Document the attempts in the source and reflect the consistent measurement in the CRF.

- 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):

- $<70 + (\text{age in years} \times 2)$ 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: Total bilirubin ≥ 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 baseline⁴²;
- Admission to an ICU;
- Death.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional outcomes defined by the CDC (listed at <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>):

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

Confirmed MIS-C definition,⁴³ as per the CDC MIS-C case definition:

- An individual <21 years of age presenting with fever ($\geq 38.0^\circ\text{C}$ 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: 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; all positive RT-PCR cases confirmed by the central laboratory will undergo BioFire testing.
- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

8.1.1. 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.

At designated sites, an additional optional whole blood sample of approximately 10 mL will be obtained prior to Dose 1, at 7 days and 6 months after Dose 2, and prior to and 1 month after Dose 3 from up to approximately 60 participants ≥ 10 years of age for isolation of PBMCs. These samples will be used on an exploratory basis to investigate the postvaccination cell-mediated immune response at these time points.

8.1.2. 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.

The participant or participant's parent(s)/legal guardian may request that the participant's 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.

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. Significant medical history and observations from any physical examination, if performed, 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 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) and use of antipyretic medication 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 will include, at a minimum, measurement of length (<2 years of age only), height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey as applicable.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Temperature, pulse rate, and RR will be assessed in all participants. BP will be assessed in participants ≥ 5 years of age.

8.2.3. Clinical Safety Laboratory Assessments

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

8.2.4. Electronic Diary

The participant or participant's parent(s)/legal guardian will be required to complete a reactogenicity e-diary through an application (see [Section 8.15](#)) installed on a provisioned device or on the personal device of the participant or participant's parent(s)/legal guardian. At the time of randomization, all participants or participants' parents/legal guardians will be asked to monitor and record local reactions, systemic events, and antipyretic medication use for 7 days following administration of the study intervention (Dose 1, Dose 2, and Dose 3). 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 if reported in the e-diary.

Those participants who originally received placebo and then received BNT162b2 will not complete a reactogenicity e-diary but will have their local reactions and systemic events detected and reported as AEs in accordance with [Section 8.3.1](#).

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, systemic events, or use of antipyretic medication 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.

The investigator or designee will be required to collect the participant's e-diary or assist the participant's parent(s)/legal guardian to delete the study application from his or her own personal device upon approval of protocol amendment 8.

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 US FDA CBER guidelines on toxicity grading scales for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials.⁴⁰

8.2.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants or participants' parents/legal guardians will be asked to assess redness, swelling, and pain/tenderness at the injection site and to record the symptoms in the reactogenicity e-diary daily for 7 days (Days 1 through 7) after each vaccination.

If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant or participant's parents/legal guardians 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 caliper units (measuring device units; range: 1 to 14 caliper units for participants <12 years of age and 1 to 20 caliper units in participants ≥12 years of age) for the first 7 days following vaccination (Days 1 through 7), and then categorized as mild, moderate, or severe using the scale shown in [Table 8](#). 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 years of age as absent, mild, moderate, or severe according to the grading scale in [Table 8](#). Tenderness at the injection site will be assessed for participants <2 years of age as absent, mild, moderate, or severe according to the grading scale in [Table 8](#).

If redness or swelling >14 caliper units for participants <12 years of age or >20 caliper units for participants ≥12 years of age 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. If Grade 3 pain or tenderness 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 is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify 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 8. Local Reaction Grading Scale

	Participant Age	Mild (Grade 1)	Moderate (Grade 2)	Severe ^a (Grade 3) ^a	Potentially Life Threatening (Grade 4) ^b
Pain at the injection site	≥2 Years	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain (tenderness) at the injection site
Tenderness at injection site	<2 Years	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at the injection site
Redness	<12 Years	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device unit) = >2.0 to 7.0 cm	>14 caliper units (or measuring device unit) = >7 cm	Necrosis or exfoliative dermatitis
	≥12 Years	5 to 10 caliper units (or measuring device units) = >2.0 to 5.0 cm	11 to 20 caliper units (or measuring device units) = >5.0 to 10.0 cm	>20 caliper units (or measuring device units) = >10 cm	Necrosis or exfoliative dermatitis
Swelling	<12 Years	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
	≥12 Years	5 to 10 caliper units (measuring device units) = >2.0 cm to 5.0 cm	11 to 20 caliper units (measuring device units) = >5.0 cm to 10.0 cm	>20 caliper units (or measuring device units) = >10 cm	Necrosis

- a. Parent(s)/legal guardians of participants <12 years of age experiencing local reactions >14 caliper units (>7 cm) and participants or parent(s)/legal guardians of participants ≥12 years of age experiencing local reactions >20 caliper units (>10 cm) are to be contacted by the study site. An unscheduled visit may be required.
- b. Only an investigator or qualified designee is able to 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 10.3.3](#).

8.2.4.3. Systemic Events

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify 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.

8.2.4.3.1. Participants ≥ 2 Years of Age

During the reactogenicity e-diary reporting period, the participant or participant's parent(s)/legal guardian 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 by the participant or participant's parent(s)/legal guardian as absent, mild, moderate, or severe according to the grading scale in Table 9.

Table 9. Systemic Event Grading Scale for Participants ≥ 2 Years of Age

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)^a
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 9. Systemic Event Grading Scale for Participants ≥ 2 Years of Age

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)^a
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. Only an investigator or qualified designee is able to 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 10.3.3](#).

8.2.4.3.2. Participants <2 Years of Age

During the reactogenicity e-diary reporting period, the participant's parent(s)/legal guardian will be asked to assess decreased appetite, drowsiness, and irritability and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant's parent(s)/legal guardian as absent, mild, moderate, or severe according to the grading scale in Table 10.

Table 10. Systemic Event Grading Scale for Participants <2 Years of Age

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)^a
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite (loss of appetite)
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued interfering with daily activity	Disabling; not interested in usual daily activity	Emergency room visit or hospitalization for severe drowsiness (increased sleep)
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability (fussiness)

Abbreviation: IV = intravenous.

- a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 systemic events will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale as detailed in [Section 10.3.3](#).

8.2.4.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure temperature at home. Temperatures will be taken orally for participants ≥ 2 years of age, and axillary for participants < 2 years of age. 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 periods when fever is suspected. Fever is defined as a temperature of $\geq 38.0^{\circ}\text{C}$ (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 11 during analysis.

If a fever of $\geq 39.0^{\circ}\text{C}$ (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as $> 40.0^{\circ}\text{C}$ ($> 104.0^{\circ}\text{F}$). If a participant experiences a confirmed fever $> 40.0^{\circ}\text{C}$ ($> 104.0^{\circ}\text{F}$), the investigator must immediately notify 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 11. Scale for Fever

Range
$\geq 38.0\text{--}38.4^{\circ}\text{C}$ ($100.4\text{--}101.1^{\circ}\text{F}$)
$> 38.4\text{--}38.9^{\circ}\text{C}$ ($101.2\text{--}102.0^{\circ}\text{F}$)
$> 38.9\text{--}40.0^{\circ}\text{C}$ ($102.1\text{--}104.0^{\circ}\text{F}$)
$> 40.0^{\circ}\text{C}$ ($> 104.0^{\circ}\text{F}$)

8.2.4.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 through Day 7).

8.2.5. Phase 1 Stopping Rules

The following stopping rules apply by age group and are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1 in each age group, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for all dose levels in the impacted age group.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162b2. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b2 dose levels within an age group will contribute to stopping rules together.

Stopping Rule Criteria for Each BNT162b2 Dose Level:

1. If any participant vaccinated with the BNT162b2 candidate at any dose level develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
2. If any participant vaccinated with the BNT162b2 candidate at any dose level develops a Grade 4 local reaction or systemic event after vaccination (see [Section 8.2.4](#)) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
3. If any participant vaccinated with the BNT162b2 candidate at any dose level develops a fever $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$) for at least 1 daily measurement after vaccination (see [Section 8.2.4](#)) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
4. If any 2 participants vaccinated with the BNT162b2 candidate at any dose level within the same age group report the same or similar severe (Grade 3) AE after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.6. Randomization and Vaccination After a Stopping Rule Is Met in Phase 1

Once the IRC and DMC have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

8.2.7. Pregnancy Testing

Pregnancy tests may be urine or serum tests but 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. In the case of a positive pregnancy test for a female participant, it is a responsibility of investigator to share the information with the participant or participant's parent(s)/legal guardian.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in [Appendix 3](#).

AEs will be reported by the participant or participant's parent(s)/legal guardian.

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](#)).

Each participant or participant's parent/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

Any Participant Enrolled Before Protocol Amendment 6

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant or participant's 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 and Dose 4 (Phase 2/3 selected-dose and obtaining-serum-samples-for-potential-troponin I-testing [≥ 5 to < 12 years old] participants who originally received placebo only) as per the [SoA](#) for each portion of the study.

SAEs will be collected from the time the participant or participant's parent(s)/legal guardian provides informed consent through 6 months after Dose 2 and Dose 4 (Phase 2/3 selected-dose and obtaining-serum-samples-for-potential-troponin I-testing (≥ 5 to < 12 years old) participants who originally received placebo only) as per the [SoA](#) for each portion of the study.

The active collection period will restart for those participants who receive a third dose of BNT162b2 (Dose 3/Dose 5) from the time the participant's parent(s)/legal guardian provides informed consent for that dose and continue through and including 1 month after Dose 3/Dose 5. SAEs will be collected from the time the participant's parent(s)/legal guardian provides informed consent for the third dose of BNT162b2 and continue through approximately 6 months after Dose 3/Dose 5.

Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards

For those participants ≥ 6 months to < 5 years of age enrolled in the Phase 2/3 selected-dose portion of the study from protocol amendment 6 onwards, the time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant's 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 3.

SAEs will be collected from the time the participant's parent(s)/legal guardian provides informed consent through 6 months after Dose 3.

Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Who Originally Receive Placebo:

For participants who originally receive placebo and go on to receive BNT162b2 as Doses 4, 5, and 6, the time period for actively eliciting and collecting AEs and SAEs will restart from the receipt of the first dose of BNT162b2 (Dose 4) through and including 1 month after Dose 6. SAEs will be collected from the time of receipt of the first dose of BNT162b2 (Dose 4) through approximately 6 months after Dose 6.

In addition, for all participants, any AEs occurring in the 48 hours following each blood draw and nasal swab collection outside of the active AE collection period must be recorded on the CRF.

Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing: Participants ≥ 12 to < 16 Years of Age Enrolled From Protocol Amendment 7:

For those participants ≥ 12 to < 16 years of age enrolled in the Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing portion of the study from protocol amendment 7 onwards, the time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant’s 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 3.

SAEs will be collected from the time the participant’s parent(s)/legal guardian provides informed consent through 6 months after Dose 3.

Adverse Events of Special Interest:

- **All participants:** Confirmed diagnosis of myocarditis or pericarditis. See [Section 8.14](#) for additional procedures for monitoring potential myocarditis or pericarditis.
- **Participants in the obtaining-serum-samples-for-potential-troponin I-testing portion of the study:** Confirmed COVID-19 (clinical signs/symptoms and positive SARS-CoV-2 NAAT test) or MIS-C diagnosis (SARS-CoV-2–positive test) will be collected as an AESI from the time the participant provides informed consent until study completion.

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 and Pfizer concurs with that assessment.

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

If the participant, participant who provided assent in any phase of the study or the participant’s parent(s)/legal guardian withdraws from the study and also withdraws consent/assent for the collection of future information, the active collection period ends when consent/assent is withdrawn.

If a participant definitively 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 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: For participants in the dose-finding or selected-dose portions, potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) and trigger an illness visit should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints. Symptoms that do not meet the criteria for a potential COVID-19/MIS-C illness should be recorded as AEs during the AE collection period.

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 3](#). 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 3](#).

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/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 3](#).

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 towards 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. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure 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 exposure during pregnancy:
 - 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 the last dose 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 preprocedure 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 with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Reporting Form. Since the information 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 is 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 for Dose-Finding/Selected-Dose Participants

Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19/MIS-C illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 business day.

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.

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.

8.3.8. Adverse Events of Special Interest

This section specifies AESIs that may be detected during the study:

- Confirmed diagnosis of myocarditis or pericarditis (all participants). See [Section 8.14](#) for additional procedures for monitoring of potential myocarditis or pericarditis.
- Confirmed COVID-19 diagnosis (clinical signs/symptoms and positive SARS-CoV-2 NAAT test) (applicable to obtaining-serum-samples-for-potential-troponin I-testing participants only).

- Confirmed MIS-C diagnosis (applicable to obtaining-serum-samples-for-potential-troponin I-testing participants only).

All AESIs must be reported as AEs or SAEs following the procedures described in [Section 8.3.1](#) through [Section 8.3.4](#). An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

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.

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. 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.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in [Section 8.1.1](#).

8.10. Health Economics

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

8.11. Study Procedures

Unless stated otherwise, all study visits are intended to be conducted in-person at the study site. If this is not possible, because of local circumstances related to the COVID-19 pandemic, study procedures that do not require in-person participant contact may be performed by telehealth. 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. Irrespective of the nature of the contact, all visit procedures are expected to be performed on the same day.

8.11.1. Phase 1 Dose-Finding Portion

8.11.1.1. Visit 1 – Dose 1 (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur in 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the day of vaccination. Ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination and on the day of the vaccination.

- 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 medical history of clinical significance.
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#), and obtain the timing for routine childhood immunizations.
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, measurement of length (<2 years of age only), height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain the participant's randomization number and study intervention allocation using the IRT system.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff) and provide nasal swab, media, and instructions to the participant's parent(s)/legal guardian on the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants <2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Issue a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.15](#)), and assist the participant's parent(s)/legal guardian in downloading the study application onto his or her own device or issue a provisioned device if required.
 - Provide instructions on reactogenicity e-diary completion and ask the 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.
 - Provide instructions on COVID-19/MIS-C illness e-diary completion and ask the participant's parent(s)/legal guardian to complete the COVID-19/MIS-C illness e-diary if the participant is diagnosed with COVID-19/MIS-C or has possible new or increased symptoms, and when a reminder is received, at least weekly. See [Section 8.15](#) for further details.
- Ask the participant's parent(s)/legal guardian, as appropriate, 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 $>39.0^{\circ}\text{C}$ ($>102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if a medically attended event (eg doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any symptoms as detailed in [Section 8.13](#).
- 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 e-diary to the next visit.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.1.2. Visit 2 – Dose 2 (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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 the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant's parent/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'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 $\geq 39.0^{\circ}\text{C}$ ($> 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring > 14 caliper units (or > 7 cm).

- Grade 3 pain or tenderness at the injection site.
- Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.1.3. Visit 3 – 7-Day Follow-up Visit (1 Week After Dose 2, 6 to 8 Days After Visit 2)

- Review the participant's reactogenicity e-diary data.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.4. Visit 4 – 1-Month Follow-up Visit (28 to 35 Days After Visit 2)

This visit can be performed as a telephone visit if the study procedure is not required for the participant.

- 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.

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

8.11.1.5. Visit 5 – 6-Month Follow-up Visit (175 to 189 Days After Visit 2)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.6. Visit 5A – Dose 3 (At Least 175 Days After Visit 2 for Participants ≥ 5 to <12 Years Old OR At Least 60 Days After Visit 2 for Participants ≥ 6 Months to <5 Years Old)

Before any study-related procedures are performed, voluntary, written, study-specific informed consent (via an ICD addendum) and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. Exclusion criterion 1 (Phase 1 only: past clinical or microbiological diagnosis of COVID-19) is not applicable for Dose 3. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#), and obtain the timing for routine childhood immunizations.
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff) and provide nasal swab, media, and instructions to the participant's parent(s)/legal guardian on the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.

- For participants <2 years of age, into the anterior thigh muscle of the (preferably) left leg.
- Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Issue a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.15](#)) and assist the participant's parent(s)/legal guardian in downloading the study application onto his or her own device or issue a provisioned device if required.
 - Provide instructions on reactogenicity e-diary completion and ask the 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.
 - Provide instructions on COVID-19/MIS-C illness e-diary completion and ask the participant's parent(s)/legal guardian to complete the COVID-19/MIS-C illness e-diary if the participant is diagnosed with COVID-19/MIS-C or has possible new or increased symptoms, and when a reminder is received, at least weekly. See [Section 8.15](#) for further details.
- Reactivate the reactogenicity e-diary.
- Ask the participant's parent(s)/legal guardian, as appropriate, 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 $\geq 39.0^{\circ}\text{C}$ ($>102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.

- Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if a medically attended event (eg doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any symptoms as detailed in [Section 8.13](#).
- 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 e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.1.7. Visit 5B – Dose 3 1-Month Follow-Up Visit (28 to 35 Days After Visit 5A)

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).

- Collect a blood sample (approximately 5 mL) for immunogenicity testing. Note: This blood draw is not applicable for participants as they are eligible to participate in the C4591048 study. Visits 5B, 5C, and 6 may now be conducted as a clinic visit or a telephone visit for these participants.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 5C – Dose 3 6-Month Follow-Up Visit (175 to 189 Days After Visit 5A)

- Record SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing. Note: This blood draw is not applicable for participants as they are eligible to participate in the C4591048 study. Visits 5B, 5C, and 6 may now be conducted as a clinic visit or a telephone visit for these participants.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 6 – 12-Month Follow-up Visit (350 to 378 Days After Visit 5A)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point.

- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing. Note: This blood draw is not applicable for participants as they are eligible to participate in the C4591048 study. Visits 5B, 5C, and 6 may now be conducted as a clinic visit or a telephone visit for these participants.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Collect the participant's e-diary or assist the participant or participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Inform the participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.2. Phase 2/3 Selected-Dose Portion

8.11.2.1. Visit 1 – Dose 1 (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the day of vaccination. Ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- 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. For participants ≥ 6 months to < 2 years of age, breast-feeding data should also be collected (this data only needs to be collected once).
- Obtain the participant's medical history of clinical significance.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- For participants ≥ 6 months to < 2 years of age, collect maternal COVID-19 immunization data for any COVID-19 vaccines given during pregnancy (these data only need to be collected once). Prior to collection of maternal COVID-19 vaccination data, the biological mother of the participant should sign the Release of Maternal COVID-19 Vaccination Information Form ([Section 8.17](#)).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including at a minimum, measurement of height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.

- On the day of and prior to vaccination, obtain the participant's randomization number and study intervention allocation number using the IRT system.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff) and provide nasal swab, media, and instructions to the participant or participant's parent(s)/legal guardian on the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
- On the day of and prior to vaccination, at designated sites participating in collection of blood samples for description of cell-mediated immune responses, the following additional procedures may be completed for participants ≥ 10 years of age:
 - Obtain written informed consent from parent(s)/legal guardian (and assent from the participant, if appropriate) agreeing to collection of the additional blood sample.
 - Collect a whole blood sample of approximately 10 mL for PBMC isolation.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Issue a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary technologies available for this study (see [Section 8.15](#)), and assist the participant's parent(s)/legal guardian in downloading the study application onto his or her own device or issue a provisioned device if required.
- Provide instructions on reactogenicity e-diary completion and ask the 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.
- Provide instructions on COVID-19/MIS-C illness e-diary completion and ask the participant's parent(s)/legal guardian to complete the COVID-19/MIS-C illness e-diary if the participant is diagnosed with COVID-19/MIS-C or has possible new or increased symptoms, and when a reminder is received, at least weekly. See [Section 8.15](#) for further details.
- Ask the 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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- 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.

8.11.2.2. Visit 2 – Dose 2 (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring > 14 caliper units (or > 7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.2.3. Visit 3 – 1-Week Follow-up Visit (After Visit 2) (6 to 8 Days After Visit 2): Only for Those Participants Having Blood Drawn for PBMC Isolation

This visit should only be conducted for participants who provided consent for collection of additional blood samples for PBMC isolation.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Collect a whole blood sample of approximately 10 mL for PBMC isolation.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.4. Visit 4 – 1-Month Follow-up Visit (After Visit 2) (28 to 35 Days After Visit 2)

This visit can be performed as a telephone visit if the study procedure is not required for the participant.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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. Collect the caliper device.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).

- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.11.2.5. Visit 4A – Dose 3 (At Least 60 Days After Visit 2): Only for Participants ≥6 Months to <5 Years of Age

Before any study-related procedures are performed, voluntary, written, study-specific informed consent (via an ICD addendum) and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

If protocol amendment 6 is implemented before the participant has completed Visit 5, the participant's parent(s)/legal guardian should be offered the consent addendum to receive a blinded third dose. If the participant's parent(s)/legal guardian refuses to sign the consent addendum, the participant should continue to Visit 5 and complete study procedures and unblinding. Following unblinding, the consent addendum should be reoffered. If the participant's parent(s)/legal guardian refuses any further vaccinations, then the participant should be withdrawn having completed the 6-month post-Dose 2 safety follow-up.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.

- Blinded site 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- 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.

8.11.2.6. Visit 4B – Dose 3 1-Month Follow-up Visit (28 to 35 Days After Visit 4A): Only for Participants ≥ 6 Months to < 5 Years of Age

Note: If Visit 4B is projected to occur after the planned Visit 5, then Visit 4B should be conducted and Visit 5 should not be conducted.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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. Collect the caliper device.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- In the scenario where Visit 4B is projected to occur after the planned Visit 5 and Visit 5 is not conducted, unblind the participant for the remainder of the study visits:
 - If the participant previously received BNT162b2, future visits should be conducted according to [Section 8.11.3](#).
 - If the participant originally received placebo, future visits should be conducted according to [Section 8.11.5](#).

- Following planned unblinding, any participant originally assigned to placebo who/whose parent/legal guardian declines the opportunity to receive BNT162b2 as part of the study, and the participant has therefore not received any active vaccine, should be withdrawn from the study. Those participants/participant's parent/legal guardians who decline the opportunity for the participant to receive a third dose of BNT162b2 as part of the study should be withdrawn from the study once the participant has reached 6 months after Dose 2.

8.11.2.7. Visit 5 – 6-Month Follow-up Visit (175 to 189 Days After Visit 2)

- For participants included to enlarge the size of the pediatric safety database and for participants under 5 years of age at enrollment, contact the participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing.
 - Not required for the additional 4500 participants included to enlarge the size of the pediatric safety database or for participants under 5 years of age at enrollment.
- Collect a whole blood sample of approximately 10 mL for PBMC isolation if the participant's parent(s)/legal guardian has provided consent to do so.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Unblind the participant for the remainder of the study visits;
 - If the participant previously received BNT162b2 and was ≥ 5 to < 12 years old at the time of enrollment, the participant will complete Visit 5A and Visit 5B on this schedule (Dose 3 administered at Visit 5A and Dose 3 1-month follow-up at Visit 5B).

- If the participant previously received BNT162b2 and was ≥ 6 months to < 5 years old at the time of enrollment, the participant will complete Visit 4A and Visit 4B on this schedule (Dose 3 administered at Visit 4A and completing Dose 3 1-month follow-up at Visit 4B).
- If the participant originally received placebo, move the participant to [Section 8.11.4](#) for his or her remaining visits if he or she has crossed over prior to protocol amendment 6. If the participant is ≥ 6 months to < 5 years old and crossing over to active vaccine after protocol amendment 6, move the participant to [Section 8.11.5](#) for the remaining visits.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.2.8. Visit 5A – Dose 3 (At Least 175 Days/140 Days in the US After Visit 2): Only for Participants ≥ 5 to < 12 Years of Age

Before any study-related procedures are performed, voluntary, written, study-specific informed consent (via an ICD addendum) and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

Note: If Visit 5A (Dose 3) occurs on or before Visit 5 (6-month follow-up visit after Dose 2), then Visit 5 does not need to be completed.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).

- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
- Collect a whole blood sample of approximately 10 mL for PBMC isolation (only for those participants having blood drawn for PBMC isolation).
- Unblinded site 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 instruction on this process.

- Blinded site 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- 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.

8.11.2.9. Visit 5B – Dose 3 1-Month Follow-up Visit (28 to 35 Days After Visit 5A): Only for Participants ≥ 5 to < 12 Years of Age

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing.
- Collect a whole blood sample of approximately 10 mL for PBMC isolation (only for those participants having blood drawn for PBMC isolation).
- 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. Collect the caliper device.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

8.11.3. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received BNT162b2 (≥6 Months to <12 Years Old Enrolled Before Protocol Amendment 6)

8.11.3.1. Visit X – Dose 3 6-Month Follow-Up Visit (175 to 189 Days After Visit 4A for Participants ≥6 Months to <5 Years Old OR After Visit 5A for Participants ≥5 to <12 Years Old)

This visit can be performed as a telephone visit if the study procedure is not required for the participant.

- Record SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required. Note: This blood sample will not be required for participants as of 20 October 2022.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.11.3.2. Visit Y – Dose 3 12-Month Follow-Up Visit (350 to 378 Days After Visit 4A for Participants ≥ 6 Months to < 5 Years Old OR After Visit 5A for Participants ≥ 5 to < 12 Years Old)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this visit time point.

This visit can be performed as a telephone visit if the study procedure is not required for the participant.

- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required. Note: This blood sample will not be required for participants as of 20 October 2022.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Collect the participant's e-diary or assist the participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Inform the participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.4. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥ 6 Months to < 12 Years Old Crossed Over Before Protocol Amendment 6)

8.11.4.1. Visit A – Dose 3 (175 to 189 Days After Dose 2)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Confirm that the participant meets local/national recommending criteria for receipt of BNT162b2 or another COVID-19 vaccine OR has reached the protocol unblinding time point per the SoA (175 to 189 days after Visit 2 or Visit 403).

- Confirm that the participant originally received placebo at Visit 1 (Dose 1) and Visit 2 (Dose 2). Secondary confirmation by another site staff member is required. Assess and document the participant's continued eligibility per the criteria in [Section 5](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant or participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
 - Blood draw is only for participants who become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to Visit 5.

- Not required for the additional 4500 participants included to enlarge the size of the pediatric safety database.
- On the day of and prior to vaccination, obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
- Please refer to the IP manual for further instruction on this process.
- Site 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and a dispenser/administrator updates the study intervention accountability records.

8.11.4.2. Visit B – Dose 4 (19 to 23 Days After Visit A)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant or participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Site 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's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

8.11.4.3. Visit C – 1-Month Follow-up Telephone Contact (After Dose 4) (28 to 35 Days After Visit B)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.

- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.4.4. Visit D – Dose 5 (At Least 175 Days/140 Days in the US After Visit B for Participants ≥ 5 to <12 Years Old OR At Least 60 Days After Visit B for Participants ≥ 6 Months to <5 Years Old)

Participants enrolled in the ≥ 2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥ 5 to <12 years age group (ie, third dose administered at least 6 months after the second dose).

Before any revised study-related procedures are performed per protocol amendment 6, voluntary, written, study-specific informed consent (via an ICD addendum) and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a physical examination, including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.

- Blinded site 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's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.4.5. Visit E – Dose 5 1-Month Follow-Up Telephone Contact (28 to 35 Days After Visit D)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.4.6. Visit F – Dose 5 6-Month Follow-Up Telephone Contact (175 to 189 Days After Visit D)

- This visit can be performed as a telephone visit.
- Record SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.4.7. Visit G – Dose 5 12-Month Follow-Up Visit (350 to 378 Days After Visit D)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point.

- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Request the return of the participant's e-diary or assist the participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

- Inform the participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.5. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo (≥6 Months to <5 Years Old Crossed Over After Protocol Amendment 6)

8.11.5.1. Visit A101 – Dose 4 (175 to 189 Days After Visit 2 or Visit 403)

For participants enrolled prior to protocol amendment 6 (SoA in [Section 1.3.2](#)) and crossed over to active vaccine after protocol amendment 6: If an ICD addendum for the 3-dose series has not been signed at a prior visit, follow the procedures below:

Before any study-related procedures are performed, voluntary, written, study-specific informed consent (via an ICD addendum) and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Confirm that the participant meets local/national recommending criteria for receipt of BNT162b2 or another COVID-19 vaccine OR has reached the protocol unblinding time point per the SoA (175 to 189 days after Visit 2 or Visit 403).
- Confirm that the participant originally received placebo for Dose 1, Dose 2, and Dose 3 in either the SoA in [Section 1.3.2](#) or the SoA in [Section 1.3.2.4](#), as appropriate. Secondary confirmation by another site staff member is required. Assess and document the participant's continued eligibility per the criteria in [Section 5](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.

- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant or participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
 - Blood draw is only required for participants enrolled after protocol amendment 6 (SoA in [Section 1.3.2.4](#), Visit 401 sequence). Blood draw is not required for those participants enrolled prior to protocol amendment 6 (SoA in [Section 1.3.2](#), Visit 1 sequence).
- On the day of and prior to vaccination, obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Site 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and a dispenser/administrator updates the study intervention accountability records.

8.11.5.2. Visit B102 – Dose 5 (19 to 23 Days After Visit A101)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).

- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant or participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Site 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's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and a dispenser/administrator updates the study intervention accountability records.

8.11.5.3. Visit C103 – Dose 6 (At Least 175 Days/140 Days in the US After Visit B102 for Participants ≥ 5 to <12 Years Old OR 56 to 70 Days After Visit B102 for Participants ≥ 6 Months to <5 Years Old)

Participants enrolled in the ≥ 2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will follow the same dose interval as the ≥ 5 to <12 years age group (ie, third dose administered at least 6 months after the second dose).

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant or participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.

- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Site 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's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and a dispenser/administrator updates the study intervention accountability records.

8.11.5.4. Visit D104 – 1-Month Follow-Up Telephone Contact (28 to 35 Days After Visit C103)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record nonstudy vaccinations as described in [Section 6.5](#).

- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.5.5. Visit E105 – 6-Month Follow-Up Telephone Contact (175 to 189 Days After Visit C103)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.5.6. Visit F106 – 12-Month Follow-Up Telephone Contact (350 to 378 Days After Visit C103)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point.

- Contact the participant's parent(s)/legal guardian by telephone.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.5.7. Visit G107 – 18-Month Follow-Up Visit (532 to 560 Days After Visit C103)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point.

- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Request the return of the participant's e-diary or assist the participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Inform the participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.6. Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled from Protocol Amendment 6 Onwards

8.11.6.1. Visit 401 – Dose 1 (Day 1)

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

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the day of vaccination. Ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- 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. For participants ≥ 6 months to < 2 years of age, breast-feeding data should also be collected (this data only needs to be collected once).
- Obtain the participant's medical history of clinical significance.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- For participants ≥ 6 months to < 2 years of age, collect maternal COVID-19 immunization data for any COVID-19 vaccines given during pregnancy (these data only need to be collected once). Prior to collection of maternal COVID-19 vaccination data, the biological mother of the participant should sign the Release of Maternal COVID-19 Vaccination Information Form ([Section 8.17](#)).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).

- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, obtain the participant's randomization number and study intervention allocation number using the IRT system.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff) and provide nasal swab, media, and instructions to the participant or participant's parent(s)/legal guardian on the technique for collecting a nasal swab at home.
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Issue a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.15](#)) and assist the participant's parent(s)/legal guardian in downloading the study application onto his or her own device or issue a provisioned device if required.

- Provide instructions on reactogenicity e-diary completion and ask the 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.
- Provide instructions on COVID-19/MIS-C illness e-diary completion and ask the participant's parent(s)/legal guardian to complete the COVID-19/MIS-C illness e-diary if the participant is diagnosed with COVID-19/MIS-C or has possible new or increased symptoms, and when a reminder is received, at least weekly. See [Section 8.15](#) for further details.
- Ask the 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 $\geq 39.0^{\circ}\text{C}$ ($>102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.6.2. Visit 402 – Dose 2 (19 to 23 Days After Visit 401)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:

- For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
- For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
- Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $> 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring > 14 caliper units (or > 7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.6.3. Visit 403 – Dose 3 (56 to 70 Days After Visit 402)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).

- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention:
 - For participants ≥ 2 years of age, into the deltoid muscle of the (preferably) nondominant arm.
 - For participants < 2 years of age, into the anterior thigh muscle of the (preferably) left leg.
 - Please refer to the IP manual for further instruction on this process.
- Blinded site 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring > 14 caliper units (or > 7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.6.4. Visit 404 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 403)

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- 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. Collect the caliper device.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required.

- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.6.5. Visit 405 – 6-Month Follow-Up Visit (175 to 189 Days After Visit 403)

- Record AEs and SAEs as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required. Note: This blood sample will not be required for participants as of 20 October 2022.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Unblind the participant for the remainder of the study visits;
 - If the participant previously received BNT162b2, future visits should be conducted according to Section 8.11.7.
 - If the participant originally received placebo, future visits should be conducted according to [Section 8.11.5](#).
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.7. Phase 2/3 Selected-Dose Portion: Participants ≥ 6 Months to < 5 Years Old Enrolled From Protocol Amendment 6 Onwards Who Originally Received BNT162b2

8.11.7.1. Visit X1 – Dose 3 12-Month Follow-Up Visit (350 to 378 Days After Visit 403)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point.

This visit can be performed as a telephone visit if the study procedure is not required for the participant.

- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required. Note: This blood sample will not be required for participants as of 20 October 2022.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator (this could be via the COVID-19/MIS-C illness e-diary) immediately if the participant experiences any acute symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.

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

8.11.7.2. Visit Y1 – Dose 3 18-Month Follow-Up Visit (532 to 560 Days After Visit 403)

This visit should not be performed when protocol amendment 8 is approved and participants are informed of early study completion prior to reaching this time point.

This visit can be performed as a telephone visit if the study procedure is not required for the participant.

- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing if the participant is in the group where blood collection at this visit is required. Note: This blood sample will not be required for participants as of 20 October 2022.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).
- Collect the participant's e-diary or assist the participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Inform the participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.8. Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing (≥ 5 to <12 Years of Age, Placebo-Controlled, and ≥ 12 to <16 Years of Age, Open-Label)

8.11.8.1. Visit 301 – Dose 1 (Day 1)

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

guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the day of vaccination. Ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- 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 medical history of clinical significance.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain the participant's randomization number and study intervention allocation number using the IRT system.

- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff).
- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for potential troponin I level evaluation.
- Unblinded site 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 instruction on this process.
- 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.
- Record AEs and SAEs as described in [Section 8.3](#).
- Issue a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.15](#)), and assist the participant or participant's parent(s)/legal guardian in downloading the study application onto his or her own device or issue a provisioned device if required.
- Provide instructions on reactogenicity 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring >14 caliper units (or >7 cm) for participants <12 years of age and >20 caliper units (or >10 cm) for participants ≥ 12 years of age.
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.8.2. Visit 302 – Dose 2 (19 to 23 Days After Visit 301)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#).
- 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.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).

- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff).
- Unblinded site 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 instruction on this process.
- 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).

- Redness or swelling at the injection site measuring >14 caliper units (or >7 cm) for participants <12 years of age and >20 caliper units (or >10 cm) for participants ≥12 years of age.
- Grade 3 pain or tenderness at the injection site.
- Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- 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.

8.11.8.3. Visit 303 – 4-Day Follow-Up Visit (2 to 5 Days After Visit 302)

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record AEs and SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Collect a blood sample (approximately 5 mL) for potential troponin I level evaluation.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.8.4. Visit 304 – 1-Month Follow-Up Visit (28 to 35 Days After Visit 302)

- Contact the participant's parent(s)/legal guardian by telephone.
- 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. Collect the caliper device.
- Record AEs and SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.8.5. Visit 304A – Dose 3 (At Least 140 Days After Visit 302)

For participants enrolled before protocol amendment 7, before any study-related procedures are performed, voluntary, written, study-specific informed consent and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff). Review with the participant's parent(s)/legal guardian the technique for collecting a nasal swab at home.
- Unblinded site 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 instruction on this process.
- Blinded site 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.
- Reactivate the reactogenicity e-diary.
- Ensure the participant's parent(s)/legal guardian has a caliper device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the 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'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 $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring >14 caliper units (or >7 cm).
 - Grade 3 pain or tenderness at the injection site.
 - Any severe systemic event.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- 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.

8.11.8.6. Visit 304B – Dose 3 4-Day Follow-Up Visit (2 to 5 Days After Visit 304A)

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- Record AEs and SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Collect a blood sample (approximately 5 mL) for potential troponin I level evaluation.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.8.7. Visit 304C – Dose 3 1-Month Follow-Up Visit (28 to 35 Days After Visit 304A)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record AEs and SAEs as described in [Section 8.3](#).
- 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. Collect the caliper device.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).

- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.8.8. Visit 305 – Dose 3 6-Month Follow-Up Visit (175 to 189 Days After Visit 304A)

- Record SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Collect the participant's e-diary or assist the participant or participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Unblind the participant (unblinding will occur prior to the 6 months after Dose 2 if the participant becomes eligible per local or national recommendations):
 - If the participant previously received BNT162b2, complete this visit for the remainder of visit activities.
 - If the participant originally received placebo, move the participant to the procedures in [Section 8.11.9](#) for the remainder of this visit's activities and future visits.
- Inform the participant or participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.9. Phase 2/3 Assessment of Obtaining Serum Samples for Potential Troponin I Testing: Participants Who Originally Received Placebo (≥ 5 to <12 Years of Age)

8.11.9.1. Visit A1 – Dose 3 (From Recommendation or 175 to 189 Days After Dose 2)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Confirm that the participant originally received placebo at Visit 301 (Dose 1) and Visit 302 (Dose 2). Secondary confirmation by another site staff member is required. Assess and document the participant's continued eligibility per the criteria in [Section 5](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff).

- On the day of and prior to vaccination, collect a blood sample (approximately 5 mL) for potential troponin I level evaluation.
 - Blood draw is only for participants who become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to Visit 303.
- On the day of and prior to vaccination, obtain the participant's vaccine vial allocation using the IRT system.
- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - Into the deltoid muscle of the (preferably) nondominant arm.
 - Please refer to the IP manual for further instruction on this process.
- Site 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.
- Record AEs and SAEs as described in [Section 8.3](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and a dispenser/administrator updates the study intervention accountability records.

8.11.9.2. Visit B1 – Dose 4 (19 to 23 Days After Visit A1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#).
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see [Section 8.14](#)).
- If appropriate, discuss contraceptive use as described in [Section 5.3.1](#).

- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff).
- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - Into the deltoid muscle of the (preferably) nondominant arm.
 - Please refer to the IP manual for further instruction on this process.
- Site 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's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

8.11.9.3. Visit C1 – 1-Month Follow-Up Telephone Contact (After Dose 4) (28 to 35 Days After Visit B1)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record AEs and SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.9.4. Visit D1 – Dose 5 (At Least 140 Days After Visit B1)

For participants enrolled before protocol amendment 7, before any study-related procedures are performed, voluntary, written, study-specific informed consent and assent if appropriate will be obtained from the participant's parent(s)/legal guardian. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant's parent(s)/legal guardian. If the participant's parent(s)/legal guardian does not consent to administration of a third dose, the participant should be withdrawn from the study once he or she has reached 6 months after Dose 2.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs and SAEs as described in [Section 8.3](#).
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- On the day of and prior to vaccination, review and consider inclusion criteria 2 through 7 and exclusion criteria 3 through 15 prior to vaccination. If, in the investigator's judgment, vaccination is in the best interests of the participant, vaccination may proceed, even if inclusion criteria are not met and exclusion criteria are met. Such exceptions should be recorded in the participant's source documents.
- On the day of and prior to vaccination, ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- On the day of and prior to vaccination, measure the participant's vital signs (including body temperature).
- On the day of and prior to vaccination, perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record as AEs.
- On the day of and prior to vaccination, perform a urine pregnancy test on all female participants who are biologically capable of having children as described in [Section 8.2.7](#). A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of and prior to vaccination, obtain a nasal (anterior nares) swab (collected by site staff).
- Site staff member(s) will dispense/administer 1 dose of BNT162b2:
 - Into the deltoid muscle of the (preferably) nondominant arm.
 - Please refer to the IP manual for further instruction on this process.

- Site 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's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.9.5. Visit E1 – Dose 5 1-Month Follow-Up Visit (28 to 35 Days After Visit D1)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record AEs and SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Discuss contraceptive use as described in [Section 5.3.1](#).
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.9.6. Visit F1 – Dose 5 6-Month Follow-Up Visit (175 to 189 Days After Visit D1)

- Record SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).

- For participants who are HIV positive, record HIV viral load and CD4 count results from the most recent test performed (if any).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- 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.

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

If a participant or participant's parent/legal guardian reports redness or swelling >14 caliper units (or >7 cm) for participants <12 years of age and >20 caliper units (or >10 cm) for participants ≥12 years of age or Grade 3 local reaction ([Section 8.2.4.2](#)), any Grade 3 systemic event ([Section 8.2.4.3](#)), or fever ≥39.0°C (102.1°F) ([Section 8.2.4.4](#)) in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction ([Section 8.2.4.2](#)), systemic event ([Section 8.2.4.3](#)), or fever ([Section 8.2.4.4](#)) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm 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 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/tenderness (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 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.

8.13. COVID-19 and MIS-C Surveillance (Dose-Finding/Selected-Dose Participants)

COVID-19 Surveillance: If a participant experience any of the following (irrespective of perceived etiology or clinical significance), the participant or his/her parent(s)/legal guardian is instructed to contact the site immediately. Optimally within 3 days after symptom onset (and at the latest 4 days after symptom resolution), the site should schedule and conduct either an in-person or telehealth visit as soon as possible, unless it is a single symptom lasting 1 calendar day (resolves the same day or next; report as an AE during the AE time period). 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.

During the 7 days following each dose, potential COVID-19 symptoms that overlap with 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. 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; unless positive, the symptoms should be recorded not as a potential COVID-19 illness, but rather as AEs.

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 (Dose-Finding/Selected-Dose Participants): The participant's parent(s)/legal guardian may utilize a COVID-19/MIS-C illness e-diary through an application (see [Section 8.15](#)) 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;
- Diarrhea;
- Vomiting;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Inability to eat/poor feeding in participants <5 years of age;
- Abdominal pain;
- Hospitalization for a severe illness with no other alternative etiology;
- Hospitalization due to confirmed COVID-19 infection.

8.13.1. 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'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 AE/SAEs as appropriate, as described in [Section 8.3](#). Note: Potential COVID-19/MIS-C illnesses and their sequelae that are consistent with the clinical endpoint definition ([Section 8.1](#)) should not be recorded as AEs/SAEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (anterior nares) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant's parent(s)/legal guardian to self-collect a nasal (anterior nares) swab and ship for assessment at the central laboratory. **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 7⁴¹;
 - $\text{SpO}_2 \geq 92\%$ on room air or $>50\%$ FiO_2 to maintain $\geq 92\%$, or $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg);
 - 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) $< 70 + (\text{age in years} \times 2)$ 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 (total bilirubin ≥ 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 baseline⁴²
- 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 (anterior nares) 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.

8.13.2. Potential COVID-19/MIS-C Convalescent Visit (28 to 35 Days After Potential COVID-19 Illness Visit)

- Prior to protocol amendment 2, a COVID-19 convalescent visit was required 28 to 35 days after each potential COVID-19 illness visit. Sufficient data have now been accrued from these visits, so the requirement has been removed from the protocol.

8.14. 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.

8.15. Communication and 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 or participant's parent(s)/legal guardian is maintained so that safety events or 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 application, 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 or her own device 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 or participant's parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see [Section 8.13](#)).

- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- 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 illness e-diary, the investigator or designee is required to contact the participant or participant's parent(s)/legal guardian to ascertain the reason and also to obtain details of any missed events.

8.16. SARS-CoV-2 NAAT Nasal (Anterior Nares) Swab Results

Nasal (anterior nares) swabs for SARS-CoV-2 NAAT are obtained at:

- On the day of and before administration of any study vaccination: To determine whether a participant will be included in analyses of those with no serological or virological evidence (prior to 7 days after receipt of Dose 2) 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.

Central laboratory-generated positive results from the vaccination visit swabs, and all results from the 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 healthcare providers at a licensed clinical laboratory when the participant exhibits potential COVID-19 symptoms or otherwise receives a positive result and should be counseled on whether to take any precautionary measures pending confirmatory testing.

Phase 1 participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows (note: not applicable to Dose 3):

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 1; therefore, administration of Dose 2 should proceed as normal.
- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 1; therefore, Dose 2 should not be given but the participant should remain in the study.

8.17. Maternal COVID-19 Vaccination Data

At Visit 1, or at the next opportunity for those participants already enrolled, maternal COVID-19 vaccination data, to include any COVID-19 vaccines given during pregnancy, should be collected for participants ≥ 6 months to < 2 years of age.

Prior to collection of maternal COVID-19 vaccination data, the biological mother of the participant should sign the Release of Maternal COVID-19 Vaccination Information Form.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in an 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. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to the primary, secondary, and exploratory objectives for Phase 1 and Phase 2/3 are described in the table in [Section 3](#).

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.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population ([Section 9.3](#)). These estimands estimate the vaccine effect in the hypothetical settings where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to $0.5 \times \text{LLOQ}$ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on the evaluable efficacy population ([Section 9.3](#)). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed for the all-available efficacy populations. Missing laboratory results will not be imputed.

9.1.2. Statistical Hypothesis

9.1.2.1. Statistical Hypothesis Evaluation for Immunogenicity

The primary immunogenicity objective in Phase 2/3 is to immunobridge the immune response elicited by prophylactic BNT162b2 at the dose level selected between Phase 2/3 participants in each age group (participants ≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years of age) at 1 month after Dose 2 or 1 month after Dose 3 (≥ 2 to <5 years and ≥ 6 months to <2 years of age) and participants 16 to 25 years of age at 1 month after Dose 2 from Phase 2/3 of the C4591001 study. The evaluable immunogenicity population will be used for the following hypotheses testing:

$$H_{01}: \ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$$

$$H_{02}: p_2 - p_1 \leq -10\%$$

where $\ln(0.67)$ corresponds to a 1.5-fold margin for immunobridging, and $\ln(\mu_2)$ and $\ln(\mu_1)$ are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients in each younger age group (≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years of age) measured 1 month after Dose 2 (or Dose 3) and in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study measured 1 month after Dose 2, respectively. For the seroresponse endpoint, p_2 and p_1 are the (true) proportions of participants achieving seroresponse in each younger age group and the 16 to 25 years age group from Phase 2/3 of the C4591001 study, respectively.

Seroresponse is defined as achieving ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of $\geq 4 \times$ LLOQ is considered seroresponse.

The hypothesis related to primary objectives for each age group will be evaluated separately. Within each age group, the hypothesis H_{01} and H_{02} will be tested sequentially in the order as specified.

- Immunobridging success based on GMR will be declared for an age group if the lower limit of the 95% CI for the GMR (younger age group to the 16 to 25 years age group from the C4591001 study) is >0.67 and the point estimate of the GMR is ≥ 0.8 .
- Immunobridging success based on the seroresponse difference will be declared if the lower limit of the 95% CI for the difference in percentages of participants with seroresponse is $>-10\%$.

Since seroresponse is not directly linked to an antibody level associated with protection against COVID-19, if the seroresponse endpoint nearly misses the noninferiority criteria, the totality of evidence will be evaluated, including RCDCs and the proportion of participants with neutralizing titers \geq LLOQ.

9.1.2.2. Statistical Hypothesis Evaluation for Efficacy

The secondary efficacy endpoints are to evaluate VE defined as $100 \times (1 - \text{IRR})$ in each of the 2 age groups (≥ 5 to < 12 years: after 2-dose series, ≥ 6 months to < 2 years and ≥ 2 to < 5 years combined: after 3-dose series) in the selected-dose portion of the study. The ≥ 6 months to < 2 years and ≥ 2 to < 5 years are combined for the VE evaluation because the same dose level was selected for these 2 age groups. Age groups in which immunobridging is not shown to be successful will not be included in the VE evaluation. IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group.

VE₁ represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior infection, and VE₂ represents VE for prophylactic BNT162b2 against confirmed COVID-19 regardless of evidence of prior infection. The assessment of VE will be based on testing the following hypothesis:

$$H_0: \text{VE} \leq 30\% \text{ vs } H_1: \text{VE} > 30\%$$

for VE₁ and VE₂, respectively.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis.

9.1.3. Multiplicity Considerations

For the immunogenicity objectives of immunobridging of BNT162b2 after the 2-dose series in each of the 3 age groups (≥ 5 to < 12 years, ≥ 2 to < 5 years, and ≥ 6 months to < 2 years of age) to the comparator group from Phase 2/3 of the C4591001 study, the hypothesis testing for each age group will be carried out separately. Each immunobridging analysis corresponds to a separate analysis of the respective age group, with a separate objective. The age groups are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied in the immunogenicity assessments for the 3 age groups.

Within each age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially in the order as specified.

In the ≥ 5 - to < 12 -year age group in the selected-dose portion of the study, where immunobridging success is declared, if the required number (21) of confirmed COVID-19 cases is accrued, then the secondary VE objectives, VE₁ and VE₂, will be tested sequentially in the order as stated. Thus, this sequential testing strategy controls type I error at the desired level of 2.5%.

The primary immunogenicity and secondary efficacy objectives after the 3-dose series for the ≥ 6 -month to < 2 -year and ≥ 2 - to < 5 -year age groups will be evaluated separately from the objectives after 2-dose series. The hypothesis testing for immunobridging of the ≥ 6 -month to < 2 -year and ≥ 2 - to < 5 -year age groups will be carried out separately in the same way as for the 2-dose series; no type I error adjustments will be applied for the assessments of the 2 age groups for the same reason described above. If immunobridging success is declared for both age groups, the secondary efficacy objectives will be tested sequentially in the order as stated for the 2 age groups combined.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. The Phase 1 dose-finding portion of the study includes a minimum of 16 participants receiving active vaccine per group for each dose level; 9 groups may be studied, corresponding to a total of up to 144 participants.

The Phase 2/3 selected-dose portion of the study will randomize approximately 4500 participants (randomization ratio of 2:1 so that 3000 receive active vaccine and 1500 receive placebo) for each age group, with a total of approximately 13,500 participants. The total sample size in Phase 2/3 is not based on statistical hypothesis testing.

9.2.1. Immunogenicity Objectives

9.2.1.1. Immunobridging Evaluation of 2-Dose Series

Participants with 1-month post-Dose 2 blood sample collection in Phase 2/3 of the study and a random sample of approximately 300 participants in the 16- to 25-year age group from Phase 2/3 of the C4591001 study who received BNT162b2 will be the immunogenicity subset for the primary immunobridging assessment of a 2-dose series. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants per age group will provide a power of 90.4% to declare immunobridging success of each younger to older age group in terms of neutralizing antibody GMR, 1 month after Dose 2 (see [Table 12](#)). Assuming a 25% nonevaluable rate, this will require approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) for each age group with 1-month post-Dose 2 blood sample collection in the Phase 2/3 selected-dose portion of the study to achieve 225 evaluable participants in the active vaccine group.

Table 12. Power Analysis for Immunobridging Assessment

Criteria	Standard Deviation (Log Value) ^a	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power ^b
Lower limit of 95% CI for GMR (younger age group/16- to 25-year age group) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.

- a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
- b. At a 0.05 alpha level (2-sided).

Within each age group at each dose level, assuming a true response rate of 90% in each comparator group, a sample size of 225 evaluable participants per group can achieve 92.6% power to show the immunobridging based on seroresponse rate using a 10% margin.

9.2.1.2. Immunobridging Evaluation of 3-Dose Series

For evaluation of the 3-dose series immunobridging objectives in the Phase 2/3 selected-dose evaluation portion of the study, approximately 200 participants in each of the younger age groups (≥ 6 months to < 2 years, ≥ 2 years to < 5 years) who were enrolled prior to protocol amendment 6 and received 3 doses of BNT162b2 will be selected and the same number of participants 16 to 25 years of age who received 2 doses of BNT162b2 from Phase 2/3 of the C4591001 study will be randomly selected as the immunobridging subset. To maintain blinding, approximately 100 participants in each age group from the C4591007 study and 50 participants 16 to 25 years of age from the C4591001 study who received placebo will also be selected for serology testing.

Assuming a nonevaluable rate of 35%, approximately 130 evaluable participants in each age group will contribute to the immunobridging evaluation.

Assuming that the assay standard deviation at 1 month after Dose 3 and 1 month after Dose 2 in log scale is 0.93 based on data observed in the Phase 3 third-dose portion of the C4591001 study and the GMR of the younger age group to the 16- to 25-year age group is 1, 130 evaluable participants in each age group will provide 93.3% power to demonstrate immunobridging success of each younger age group to the 16- to 25-year age group based on GMR using a 1.5-fold margin. For comparisons based on seroresponse, a 95% response rate is assumed for each comparative group at the comparative time point. With 130 evaluable participants, the study has 90.4% power to show the immunobridging based on seroresponse rate using a 10% margin.

9.2.2. Efficacy Objectives

For VE evaluation after the 2-dose series and prior to Dose 3 for the ≥ 5 - to < 12 -year age group, with a total of approximately 4500 participants ≥ 5 to < 12 years of age (3000 participants randomized to the vaccine group and 1500 participants randomized to the placebo group), assuming 25% of the participants being nonevaluable and 1.3% annual attack rate, a total of approximately 11 first confirmed COVID-19 illness cases will be observed within 6 months after vaccination. This provides approximately 35.1% power to conclude true VE $> 30\%$ with assumptions of a true VE of 80%.

For VE evaluation after the 3-dose series for the ≥ 6 months to < 5 years of age group, if immunobridging success is declared in both younger age groups (≥ 6 months to < 2 years, ≥ 2 months to < 5 years) in the selected-dose portion of the study, then VE will be assessed by combining these 2 age groups, resulting in a total of approximately 23 confirmed COVID-19 illness cases within 6 months after vaccination. Depending upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be higher, in which case accrual would be expected to be more rapid.

Since it requires at least 21 cases to achieve 77.0% power, hypothesis testing will be conducted only if at least 21 cases are accrued in the specific age groups (≥ 5 to < 12 years; ≥ 6 months to < 2 years and ≥ 2 to < 5 years combined) in which immunobridging is shown to be successful (Table 13).

Table 13. Power for Vaccine Efficacy Assessment

Power	Total Cases	Case Split ^a to Claim Success ^b (VE%)
18.6%	5	0:5 (100%)
35.1%	11	2:9 (88.9%)
77.0%	21	7:14 (75.0%)
81.5%	23	8:15 (73.3%)
85.1%	25	9:16 (71.9%)
93.8%	33	13:20 (67.5%)

Abbreviation: VE = vaccine efficacy.

- Case split numbers represent the number of cases in the active vaccine group vs the number of cases in the placebo group.
- Success criterion: lower bound of 95% CI for VE $> 30\%$.

9.2.3. Safety Assessment

For safety outcomes, Table 14 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 16 participants in a vaccine group, there is 81% probability of observing at least 1 AE.

Table 14. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=16	N=32	N=144	N=600	N=3000	N=9000
0.01%	0.00	0.00	0.01	0.06	0.26	0.59
0.02%	0.00	0.01	0.03	0.11	0.45	0.83
0.04%	0.01	0.01	0.06	0.21	0.70	0.97
0.06%	0.01	0.02	0.08	0.30	0.83	>0.99
0.08%	0.01	0.03	0.11	0.38	0.91	>0.99
0.10%	0.02	0.03	0.13	0.45	0.95	>0.99
0.15%	0.02	0.05	0.19	0.59	0.99	>0.99
0.20%	0.03	0.06	0.25	0.70	>0.99	>0.99
0.25%	0.04	0.08	0.30	0.78	>0.99	>0.99
0.30%	0.05	0.09	0.35	0.84	>0.99	>0.99
0.35%	0.05	0.11	0.40	0.88	>0.99	>0.99
0.50%	0.08	0.15	0.51	0.95	>0.99	>0.99
1.00%	0.15	0.28	0.76	>0.99	>0.99	>0.99
2.00%	0.28	0.48	0.95	>0.99	>0.99	>0.99
3.00%	0.39	0.62	0.99	>0.99	>0.99	>0.99
5.00%	0.56	0.81	>0.99	>0.99	>0.99	>0.99
7.00%	0.69	0.90	>0.99	>0.99	>0.99	>0.99
10.00%	0.81	0.97	>0.99	>0.99	>0.99	>0.99

Note: N = number of participants in a vaccine group. In the Phase 1 dose-finding portion of the study, 16 participants per dose level in each age group and a total of 144 participants are to be vaccinated. Approximately 3000 participants in each age group will receive the active vaccine at the selected dose level in the Phase 2/3 selected-dose portion of the study. A total of 9000 in the Phase 2/3 selected-dose portion of the study will receive the active vaccine at the selected dose level.

9.3. Analysis Sets

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity (2-dose)	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.

Population	Description
Evaluable immunogenicity (3-dose)	All eligible randomized participants who receive 3 doses of the vaccine to which they are randomized 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, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
Evaluable efficacy (2-dose)	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (3-dose)	All eligible randomized participants who receive 3 doses of the vaccine to which they are randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy (mITT)	Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination. Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses. Dose 3 all-available efficacy: All randomized participants who complete 3 vaccination doses.
Safety	All participants who receive at least 1 dose of the study intervention.

9.4. 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, secondary, and exploratory endpoints.

9.4.1. General Considerations

All safety and immunogenicity will be analyzed separately for each age group and each portion of the study. VE will be evaluated for the specific age groups (≥ 5 to < 12 years; ≥ 6 months to < 2 years and ≥ 2 to < 5 years combined) in which immunobridging success is declared.

CI's for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

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

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

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the vaccine group to which they were randomized. Missing laboratory results will not be imputed.

9.4.1.1. Analyses for Binary Data

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

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

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

9.4.1.2. Analyses for Continuous Data

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

9.4.1.2.1. 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.

9.4.1.2.2. 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.

9.4.1.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers in the younger age group minus that in 16- to 25-year age group) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

9.4.1.2.4. Reverse Cumulative Distribution Curves

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

9.4.2. Primary Endpoint(s)

Endpoint	Statistical Analysis Methods
Safety	<ul style="list-style-type: none">Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. 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 9.4.1.1).AEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs from Dose 1 to 1 month after Dose 2 and AEs from Dose 3 to 1 month after Dose 3 will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs during the blinded follow-up period in the Phase 2/3 selected-dose portion of the study. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if

Endpoint	Statistical Analysis Methods
	<p>there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. Analyses methods are described in Section 9.4.1.1.</p> <ul style="list-style-type: none"> SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after Dose 2 and SAEs from Dose 3 to 6 months after Dose 3 will be provided for each vaccine group. AEs and SAEs reported after the first dose of BNT162b2 will be summarized separately for participants who originally received placebo and then received BNT162b2 after unblinding. Participants who aged up in the study and received different dose levels at Dose 2 and/or Dose 3 will be summarized separately.
Immunogenicity (Phase 2/3 selected-dose portion of the study)	<p>GMR of SARS-CoV-2 neutralizing titers in participants ≥ 5 to < 12 years, ≥ 2 to < 5 years, or ≥ 6 months to < 2 years of age to those 16 to 25 years of age in Study C4591001</p> <ul style="list-style-type: none"> The GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in each younger age group (≥ 5 to < 12 years, ≥ 2 to < 5 years, and ≥ 6 months to < 2 years of age) at 1 month after Dose 2 or 1 month after Dose 3 (≥ 2 to < 5 years and ≥ 6 months to < 2 years of age) to the 16- to 25-year age group at 1 month after Dose 2, will be provided along with associated 2-sided 95% CIs (see Section 9.4.1.2.3). Only participants with no serological or virological evidence (up to 1 month after receipt of Dose 2 or Dose 3, as appropriate) of past SARS-CoV-2 infection will be included in the analysis. Immunobridging success based on GMR will be declared for an age group if the lower bound of the 2-sided 95% for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.8. <p>The difference in percentages of participants with seroresponse in participants ≥ 5 to < 12 years, ≥ 2 to < 5 years, or ≥ 6 months to < 2 years of age and those 16 to 25 years of age from Phase 2/3 of the C4591001 study</p>

Endpoint	Statistical Analysis Methods
	<ul style="list-style-type: none"> The percentages of participants with seroresponse at 1 month after Dose 2 or 1 month after Dose 3 in each younger age group (≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years) and those 16 to 25 years of age at 1 month after Dose 2 from Phase 2/3 of the C4591001 study, and the difference in percentages, will be provided along with associated 2-sided 95% CIs (see Section 9.4.1.1). Only participants with no serological or virological evidence (up to 1 month after receipt of Dose 2 or Dose 3, as appropriate) of past SARS-CoV-2 infection will be included in the analysis. Immunobridging success based on the seroresponse difference will be declared for an age group if the lower bound of the 2-sided 95% CIs for the seroresponse difference is $>-10\%$. Since seroresponse is not directly linked to an antibody level associated with protection against COVID-19, if the seroresponse endpoint nearly misses the noninferiority criteria, the totality of evidence will be evaluated, including RCDCs and the proportion of participants with neutralizing titers \geq LLOQ.

9.4.3. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Immunogenicity (Phase 1)	GMTs of SARS-CoV-2 neutralizing titers <ul style="list-style-type: none"> For SARS-CoV-2 neutralizing titers, GMTs and 2-sided 95% CIs will be provided for each vaccine group at each time point. Statistical methods are described in Section 9.4.1.2.1.
Immunogenicity (Phase 2/3 selected-dose portion of the study)	GMTs and GMFRs of SARS-CoV-2 neutralizing titers <ul style="list-style-type: none"> GMTs at each time point and GMFRs of SARS-CoV-2 neutralizing titers from before vaccination to each subsequent time point after vaccination will be provided in participants with no serological or virological evidence of past SARS-CoV-2 infection using the same statistical analysis method described above. Participants' data will be excluded from the time point that the participant has a nonnegative NAAT or N-binding antibody result.
VE (Phase 2/3 selected-dose portion of the study)	Ratio of confirmed COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group for the ≥ 5- to <12-year age group

Endpoint	Statistical Analysis Methods
	<p>Ratio of confirmed COVID-19 illness from 7 days after Dose 3 per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of Dose 3) for the active vaccine group to the placebo group for the ≥ 6-month to < 2-year and ≥ 2- to < 5-year age groups combined</p> <ul style="list-style-type: none"> • VE will be estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after Dose 2 to prior to Dose 3 (≥ 5 to < 12 years of age) or from 7 days after Dose 3 (≥ 6 months to < 2 years and ≥ 2 to < 5 years of age combined). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time. • The analysis will be based on the evaluable efficacy population and the all-available efficacy population. Missing efficacy data will not be imputed. <p>Ratio of confirmed COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group for the ≥ 5- to < 12-year age group</p> <p>Ratio of confirmed COVID-19 illness from 7 days after Dose 3 per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of Dose 3) for the active vaccine group to the placebo group for the ≥ 6-month to < 2-year and ≥ 2- to < 5-year age groups combined</p> <ul style="list-style-type: none"> • The same analysis method used for the first VE endpoint will be applied.

9.4.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
VE (Phase 2/3 selected-dose portion of the study)	<ul style="list-style-type: none"> After the hypotheses on VE have been evaluated with a sufficient number of cases accrued during the blinded follow-up, the selected-dose portion of the study will continue with blinded follow-up until the participants are unblinded at the time of being eligible for receipt of BNT162b2 or another COVID-19 vaccine according to local or national recommendations prior to Visit 5 for the ≥ 5- to <12-year age group (detailed separately, and available in the electronic study reference portal). The 2 younger age groups will receive Dose 3 and continue blinded follow-up after Dose 3. A descriptive summary of VE for confirmed COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 through the blinded follow-up period will be provided for each age group and for the ≥ 6-month to <2-year and ≥ 2- to <5-year age groups combined by including additional follow-up data during the blinded follow-up (if applicable) or at the end of the blinded follow-up period. A descriptive summary of VE for confirmed COVID-19 illness from 7 days after Dose 3 during the blinded follow-up period will be provided for each of the ≥ 6-month to <2-year and ≥ 2- to <5-year age groups. A descriptive summary of relative VE for confirmed COVID-19 illness from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 during the same calendar time interval of interest may be provided. Participants from the original active vaccine group receiving 3 doses of BNT162b2 will be compared to participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding in each age group and the ≥ 6-month to <2-year and ≥ 2- to <5-year age groups combined. A descriptive analysis of VE may be conducted for regulatory purposes prior to the required number of cases being accrued for the secondary VE hypotheses in order to facilitate overall assessment of benefit-risk by regulatory authorities. Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness after receipt of each dose of BNT162b2 will be provided for participants in each age group who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.

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Endpoint	Statistical Analysis Methods
Safety	<ul style="list-style-type: none"> Descriptive summary of all safety endpoints will be provided for children with stable HIV disease.
Immunogenicity (Phase 2/3)	<ul style="list-style-type: none"> GMTs of SARS-CoV-2 neutralizing titers along with their GMFRs will be provided in participants with and without serological or virological evidence of past SARS-CoV-2 infection using the same statistical analysis method described for the secondary immunogenicity endpoints. Empirical RCDs will be provided for SARS-CoV-2 neutralizing titers (Section 9.4.1.2.4). Descriptive summary of all immunogenicity endpoints will be performed for children with stable HIV disease.
COVID-19 cases	<ul style="list-style-type: none"> Listings of severe COVID-19 and confirmed MIS-C cases will be provided.
Immune response emerging VOCs	<ul style="list-style-type: none"> GMTs and/or GMFRs of SARS-CoV-2 VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each vaccine group. GMRs of SARS-CoV-2 VOC-neutralizing titers to reference-strain neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.
Cell-mediated immune response	<ul style="list-style-type: none"> The cell-mediated immune response and additional humoral immune response parameters to the reference strain will be summarized for the subset of participants with PBMC samples collected.
Troponin I	<ul style="list-style-type: none"> Counts and percentages of participants with elevated troponin I level at baseline and after Vaccination 2 and/or 3 will be provided if testing is indicated based upon data accrued outside of this study. The associated Clopper-Pearson 95% CIs will also be provided.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in the section below.

9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available for a given age group:

- Complete safety and immunogenicity analysis approximately 7 days after Dose 2 for Phase 1 in each age group.

- Immunogenicity data through 1 month after Dose 2 from the approximately 450 participants in the Phase 2/3 selected-dose portion of the study included in the immunobridging analysis in each age group (immunobridging analysis of SARS-CoV-2 neutralizing titers in each age group compared to the comparator group from Phase 2/3 of the C4591001 study).
- Immunogenicity data through 1 month after Dose 3 from the approximately 300 participants in the Phase 2/3 selected-dose portion of the study included in the immunobridging analysis in each of the 2 younger age groups (immunobridging analysis of SARS-CoV-2 neutralizing titers in the ≥ 6 -month to < 2 -year and ≥ 2 - to < 5 -year age groups compared to the comparator group from Phase 2/3 of the C4591001 study).
- Safety data through 1 month after Dose 2 from participants ≥ 5 to < 12 years of age in the Phase 2/3 selected-dose portion of the study enrolled before safety expansion.
- Safety data through 1 month after Dose 2 from all participants in each age group in the Phase 2/3 selected-dose evaluation or obtaining-serum-samples-for-potential-troponin I-testing portions of the study.
- Safety data through 1 month after Dose 3 from all participants in each age group in the Phase 2/3 selected-dose portion of the study.
- Complete safety or immunogenicity analysis approximately 6 months after Dose 2 for participants in each age group in the Phase 2/3 selected-dose portion of the study and complete safety analysis approximately 6 months after Dose 2 for participants in the obtaining-serum-samples-for-potential-troponin I-testing portions of the study.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 3 for participants in each age group in the Phase 2/3 selected-dose portions of the study.
- Complete safety analysis after complete data are available in each age group or at the end of the study.
- Efficacy analysis in the ≥ 5 - to < 12 -year age group when immunobridging success is declared and at least 21 cases are accrued from 7 days after Dose 2 to prior to Dose 3.
- Efficacy analysis in the ≥ 6 -month to < 2 -year and ≥ 2 - to > 5 -year age groups combined for which immunobridging success is declared when at least 21 cases from 7 days after Dose 3 are accrued in these age groups.
- Updated efficacy analysis at the end of the blinded follow-up period.

Certain analyses may be combined as 1 regulatory submission report if the data become available around the same time. Additional analyses may be conducted if required for regulatory purposes. All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, an external DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

- The responsibilities of the IRC are only in Phase 1 and will include:
- Review of safety data to permit dose finding in each age group
- Review of safety data in the case of a stopping rule being met
- Review of safety and/or immunogenicity data to:
 - Allow groups of participants in each age group to proceed
 - Select dose level(s) to proceed into Phase 2/3. Data supporting these selections, including results for neutralizing titers, and the ratio between them, will also be submitted to the US FDA for review.
- Review of any available safety and/or immunogenicity data generated during the course of this study, to determine:
 - Whether any dose level or schedule may not be started
 - Whether any dose level or schedule may be terminated early
 - Whether any dose level or schedule may be expanded to enroll more than 16 (or 32) participants per dose level or schedule
 - Whether any dose level may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule

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

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, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and 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.

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 guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (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 ICH GCP 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 course of 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/or his/her parent(s)/legal guardian as applicable and answer all questions regarding the study. The participant and/or his/her parent(s)/legal guardian as applicable 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 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 a legally authorized representative.

Participants and/or their parent(s)/legal guardian as applicable must be informed that their participation is voluntary. The participant or participant's parent(s)/legal guardian as applicable 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 participant or participant's parent(s)/legal guardian as applicable 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.

The participant and/or participant's parent(s)/legal guardian as applicable 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 participant or participant's parent(s)/legal guardian as applicable.

The participant or participant's parent(s)/legal guardian as applicable 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 participant or participant's parent(s)/legal guardian as applicable is fully informed about his or her right to access and correct his or her personal data or his or her child's personal data and to withdraw consent for the processing of his or her personal data or his or her child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian 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.

The participant or parent(s)/legal guardian as applicable must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

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

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 identification.

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. 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 European Union 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 available data from these trials 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.

10.1.6. 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.

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

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.

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.

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, and all applicable regulatory requirements.

Records and documents, including signed ICDs, 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 inspection 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.

10.1.7. 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 can be found in the study monitoring plan.

Description of the use of computerized system is documented in the data management plan.

10.1.8. 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 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.

10.1.9. 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.

10.1.10. 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 on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
<ul style="list-style-type: none"> An AE is any untoward medical occurrence in a patient or clinical study participant, 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 abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"> Any abnormal laboratory test results (hematology, clinical chemistry, 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 abnormal laboratory test results that meet any of the conditions below must be recorded as an AE: <ul style="list-style-type: none"> Is associated with accompanying symptoms. Requires additional diagnostic testing or medical/surgical intervention. Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does constitute an AE or SAE.

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Events **NOT** Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence 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 start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might 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 detained (usually involving at least an overnight stay) at the hospital or emergency ward 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.

An SAE is defined as any untoward medical occurrence that, at any dose:

d. Results in persistent 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.
- 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 patient 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

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

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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, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant 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 information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant'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 occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- 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 administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report 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 information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting 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 reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange 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 laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

Sites will be notified upon implementation of the electronic data tool collection

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
<ul style="list-style-type: none">• The primary mechanism for reporting an 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 report 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 entry of new data or changes to existing data.• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. 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 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 when engaging in any activity that allows for passage of ejaculate to another person.

10.4.2. 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 10.4.3](#))
 - 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.

10.4.3. Woman of Childbearing Potential

A woman 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.

Women 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.
 - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.

10.4.4. Contraception Methods

Contraceptive use by men or women 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.
5. Vasectomized partner:
 - 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).

10.5. Appendix 5: 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 $3 \times \text{ULN}$ should be monitored more frequently to determine if they are an “adaptor” 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 below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (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 $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ 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 $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (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 cases of Hy's law, 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 coformulated product in prescription or over-the-counter medications), recreational drug, 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 and 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.

10.6. Appendix 6: Abbreviations

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

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
app	application
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransferase
BiPaP	bilevel positive airway pressure
BNP	brain natriuretic peptide
BNT162b2 OMI	BNT162b2 OMICRON (B.1.1.529)
BP	blood pressure
CBER	Center for Biologics Evaluation and Research
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	creatinine kinase
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
CVA	cerebrovascular accident
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate

Abbreviation	Term
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
GMR	geometric mean ratio
GMT	geometric mean titer
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
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
IL-6	interleukin 6
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
IWR	interactive Web-based response
LDH	lactate dehydrogenase
LFT	liver function test

Abbreviation	Term
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
mITT	modified-intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PACL	protocol administrative change letter
PaO ₂	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SMS	short message service
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
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal

Abbreviation	Term
UK	United Kingdom
US	United States
VE	vaccine efficacy
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VOC	variant of concern
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

10.7. Appendix 7: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count ≥ 200 cells/mm³ (or percentage of $\geq 15\%$ for participants <6 years of age) within 6 months before enrollment and receiving stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥ 12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥ 6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels

In those who have had a liver biopsy performed,

- Findings that confirm the absence of significant necroinflammation

10.8. Appendix 8: Country-Specific Appendix – Applicable to Poland Only

In extenuating circumstances, a site may choose to have a protocol-trained member of the site study team to conduct an in-person study follow-up visit at the participant's location, rather than an in-person study follow-up visit at the site. The following may be performed during an in-person study visit at the participant's location:

All study-specific procedures/assessments detailed in [Section 1.3](#) and [Section 8.11](#).

Prior to scheduling an in-person study visit at the participant's location, documentation detailing how protocol-required safety and other specific clinical assessments (eg, blood draws, nasal swab collection, vital signs, physical examination, and AE monitoring) will be conducted and must be approved by Pfizer. The site study team member must be appropriately trained on the study and delegated to this duty on the Site Delegation of Duties Log.

10.9. Appendix 9: Country-Specific Appendix – Applicable to Mexico Only

Participants experiencing potential COVID-19 symptoms in Mexico, as confirmed by the investigator as indicative of COVID-19, must attend the site for a swab to be taken by site staff. Self-swabs will not be utilized in Mexico.

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