Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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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 and Young Adults

This supplement contains the following items:

1. Original Protocol page 3
2. Final Protocol (amendment 4) that is the original protocol and all cumulative amendments (shown on page 144) page 143
3. Original Statistical Analysis Plan page 354
4. Final Statistical Analysis Plan (version 4) that is the original plan and all cumulative amendments (shown on page 408) page 403

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 ≥5 TO <12 YEARS OF AGE

Study Sponsor	BioNTech
Study Conducted By	Pfizer
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Study Intervention Name:	RNA-Based COVID-19 Vaccine
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Phase:	1/2/3

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 ≥5 to <12 Years of Age

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
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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 ≥5 to <12 Years of Age

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. 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. VE from Phase 2/3 for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95%, with 8 COVID-19 cases in the active vaccine group compared to 162 COVID-19 cases in the placebo 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.

This Phase 1/2/3 study (C4591007) will evaluate up to 3 dose levels of BNT162b2 for safety, tolerability, immunogenicity, and efficacy depending on accrual of a sufficient number of cases. Phase 1 includes the dose-finding portion based on acceptable blinded safety data in the 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 this study will be selected based on the Phase 1 safety, tolerability, and immunogenicity data. Phase 2/3 includes the noninferiority comparison of immune responses in participants ≥5 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 accrual of a sufficient number of cases) will also be evaluated in Phase 2/3 of this study.

Objectives, Estimands, and Endpoints

Phase 1		
Objectives	**Estimands**	**Endpoints**
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162b2 at each dose level	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162b2 at each dose level	In participants complying with the key protocol criteria (evaluable participants): At baseline, before Dose 2, and 7 days after Dose 2, • GMTs at each time point • GMFR from before Dose 1 (baseline) to each subsequent time point after vaccination	• 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		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• Confirmed cases as per CDC criteria

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To define the safety profile of prophylactic BNT162b2 at the selected dose level in the first approximately 450 participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, from each vaccine group, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 1 month after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 at the selected dose level in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To demonstrate the noninferiority of the immune response elicited by prophylactic BNT162b2 at the selected dose level in Phase 2/3 participants without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection: • 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	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: • 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	• SARS-CoV-2 neutralizing titers

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
Secondary Immunogenicity/Efficacy:	**Secondary Immunogenicity/Efficacy:**	**Secondary Immunogenicity/Efficacy:**
To describe the immune responses elicited by prophylactic BNT162b2 at the selected dose level and persistence of immune response 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 group: At baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers
If at least 22 cases are accrued: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants 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: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up
If at least 22 cases are accrued: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants 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: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants without evidence of past SARS-CoV-2 infection	In evaluable participants without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion
Exploratory:	**Exploratory:**	**Exploratory:**
To evaluate the immune response over time to prophylactic BNT162b2 at selected dose level and persistence of immune response 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: At baseline and at 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
To evaluate the immune response (non-S) to SARS-CoV-2 in Phase 2/3 participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe COVID-19 and severe COVID-19 cases in all participants with and without serological or virological evidence of past SARS-CoV-2 infection		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• Confirmed cases as per CDC criteria
To describe the serological responses in Phase 2/3 participants to BNT162b2 at the selected dose level in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 neutralizing titers
To describe the safety and immunogenicity of prophylactic BNT162b2 at the selected dose level in children with stable HIV disease		• All safety and immunogenicity endpoints described above will be analyzed descriptively

Overall Design

This is a Phase 1/2/3 study in healthy children ≥5 to <12 years of age.

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.

Phase 1 is the open-label dose-finding portion of the study to evaluate safety, tolerability, and immunogenicity of BNT162b2 on a 2-dose (separated by approximately 21 days) schedule. Dose finding is being initiated in this study 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.

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 final BNT162b2 dose level for Phase 2/3.

Phase 2/3 will evaluate the safety, tolerability, immunogenicity, and efficacy (depending on accrual of a sufficient number of cases) of the selected dose level from Phase 1. All participants will have blood drawn at baseline prior to Dose 1 and 6 months after Dose 2.

The noninferiority comparison to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and at 1, 6, 12 (original BNT162b2 group only), and 24 months after Dose 2 (original BNT162b2 group only). In addition, efficacy against confirmed COVID-19 and against asymptomatic infection will also be assessed if at least 22 cases are accrued.

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.

Number of Participants

Phase 1 is an open-label dose-finding study that will consist of up to 3 different dose levels with 16 participants per dose level (total of 48 participants).

Phase 1 Participants			
Total	**Up to 3 Dose Levels of BNT162b2**	**Active**	**Placebo**
48	16/16/16	16	N/A

Phase 2/3 will evaluate the safety, tolerability, immunogenicity, and efficacy (depending on accrual of a sufficient number of cases) of the selected dose level from Phase 1, with a total of approximately 2250 participants. Participants will be randomized in a 2:1 ratio to receive active vaccine or placebo.

The first approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) randomized in this phase will contribute to the noninferiority comparison at 1 month after Dose 2 and will contribute to the persistence of immune response at 6 months after Dose 2. For the persistence time points of 12 and 24 months after Dose 2, approximately 70 participants in the original BNT162b2 vaccine group will have an immunogenicity blood draw in order to contribute to the analysis. All approximately 2250 participants will contribute to the VE analysis for conditional VE and asymptomatic infection. Efficacy will only be assessed if at least 22 cases are accrued.

Phase 2/3 Participants –Blood Draws for Immunogenicity/Efficacy Assessments			
	Total	**Active**	**Placebo**
Baseline blood draw	2250	1500	750
1 Month after Dose 2	450	300	150
6 Months after Dose 2	2250	1500	750
12 Months after Dose 2	70	70	N/A
24 Months after Dose 2	70	70	N/A

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

Phase 2/3 Participants – Safety and Tolerability/Efficacy Assessments		
Total	**Active**	**Placebo**
2250	1500	750

Intervention Groups and Duration

Phase 1: Dose finding will begin at the low-dose level. Dosing will commence at the mid-dose level upon confirmation of acceptable safety assessment at the low-dose level after Dose 1. The same process will be followed when moving to the high-dose level.

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. 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.

Phase 2/3: To proceed to the Phase 2/3 evaluation, safety, tolerability, immunogenicity, and efficacy (depending on accrual of a sufficient number of cases) data from 7 days after Dose 2 for the selected vaccine dose level from Phase 1 will be confirmed to be acceptable.

Duration: Participants are expected to participate for up to a maximum of approximately 26 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

Noninferiority of the immune response to prophylactic BNT162b2 in participants ≥5 to <12 years of age to the response in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. Noninferiority will be declared if the lower limit of the 95% CI for the GMR (≥5 to <12 years of age group to 16-25 year of age group from C4591001) is >0.67. A sample size of 225 evaluable participants will provide a power of 90.4% to declare noninferiority. The immunogenicity data from the active vaccine recipients in the first approximately 450 participants randomized in Phase 2/3 will be used for the noninferiority assessment.

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 against the confirmed COVID-19 illness, which is defined as VE = 100 × (1 – IRR). 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. Hypothesis testing will be conducted if at least 22 cases are accrued. With the assumption of a true VE of 75%, 22 cases will provide 70% power to conclude true VE >20%.

VE against asymptomatic infection will be evaluated descriptively. VE estimate and 2-sided 95% CI for VE will be provided using the Clopper-Pearson method.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the Study Assessments and Procedures section of the protocol for detailed 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

An unplanned potential COVID-19/MIS-C illness visit and unplanned potential COVID-19/MIS-C convalescent visit are 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.

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Unplanned**	**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**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19/ MIS-C Illness Visit[b]**	**Potential COVID-19/ MIS-C Convalescent Visit**
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**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
Obtain informed consent and assent (if appropriate)	X								
Assign participant number	X								
Obtain demography and significant medical history data	X								
Measure vital signs (including body temperature)	X	X							
Perform targeted physical examination including height and weight[c]	X	X							

Visit Number	1	2	3	4	5	6	7	Unplanned	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**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19/ MIS-C Illness Visit[b]**	**Potential COVID-19/ MIS-C Convalescent Visit**
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**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X							
Confirm use of contraceptives (if appropriate)	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 temporary delay criteria	X	X							
Confirm eligibility	X	X							
Obtain randomization number and study intervention allocation	X								
Obtain anterior nasal swab	X	X						X	
Collect blood sample for immunogenicity	~5 mL	~5 mL	~5 mL						~5 mL
Administer study intervention	X	X							
Assess acute reactions for at least 30 minutes after study intervention administration	X	X							
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X								

Visit Number	1	2	3	4	5	6	7	Unplanned	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**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19/ MIS-C Illness Visit[b]**	**Potential COVID-19/ MIS-C Convalescent Visit**
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**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
Provide a thermometer and caliper (measuring) device	X								
Ensure the participant's parent(s)/legal guardian has a caliper device and thermometer		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							
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					
Collect AEs[d]	X	X	X	X				X	X
Collect SAEs[e]	X	X	X	X	X			X	X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application							X		
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)								X	X

Visit Number	1	2	3	4	5	6	7	Unplanned	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	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19/ MIS-C Illness Visit[b]	Potential COVID-19/ MIS-C Convalescent Visit
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	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset	28 to 35 Days After Potential COVID-19/MIS-C Illness Visit
Type of Visit	Clinic	Clinic	Clinic	Clinic or Telephone	Telephone	Telephone	Clinic or Telephone	Clinic or Telehealth	Clinic

Abbreviations: CRF = case report form; MIS-C = multisystem inflammatory syndrome in children.

a. 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.
b. Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
c. Height and weight will be collected only at Visit 1.
d. 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.
e. Refer to Section 8.3.1 for the time period for collecting SAEs.

1.3.2. Phase 2/3

An unplanned potential COVID-19/MIS-C illness visit and unplanned potential COVID-19/MIS-C convalescent visit are 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.

At the 6-month (Visit 4) 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.

Visit Number	1	2	3	4	Unplanned	Unplanned
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[b]**	**Potential COVID-19/ MIS-C Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic or Telephone**	**Clinic**	**Clinic or Telehealth**	**Clinic**
Obtain informed consent and assent (if appropriate)	X					
Assign participant number	X					
Obtain demography and significant medical history data	X					
Measure vital signs (including body temperature)	X	X				
Perform targeted physical examination including height and weight[c]	X	X				
For participants who are HIV positive, record latest CD4 count and HIV viral load	X		X	X		
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X				
Confirm use of contraceptives (if appropriate)	X	X	X			
Collect nonstudy vaccine information	X	X	X	X		
Collect prohibited medication use		X	X	X	X	X
Review temporary delay criteria	X	X				

Visit Number	1	2	3	4	Unplanned	Unplanned
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[b]**	**Potential COVID-19/ MIS-C Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic or Telephone**	**Clinic**	**Clinic or Telehealth**	**Clinic**
Confirm eligibility	X	X				
Obtain randomization number and study intervention allocation	X					
Obtain anterior nasal swab	X	X			X	
Collect blood sample for immunogenicity	~5 mL		~5 mL[d]	~5 mL		~5 mL
Administer study intervention	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	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					
Ensure the participant's parent(s)/legal guardian has a caliper device and thermometer		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				
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			
Collect AEs as appropriate[e]	X	X	X		X	X
Collect SAEs as appropriate[f]	X	X	X	X	X	X

Visit Number	1	2	3	4	Unplanned	Unplanned
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[b]**	**Potential COVID-19/ MIS-C Convalescent Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Clinic or Telephone**	**Clinic**	**Clinic or Telehealth**	**Clinic**
Unblind the participant and move to either Section 1.3.2.1 or Section 1.3.2.2				X		
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)					X	X

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

a. This visit may be conducted across 2 consecutive dates; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the day of vaccination.
b. Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
c. Height and weight will be collected only at Visit 1.
d. Only the first approximately 450 randomized participants will have blood drawn at 1 month after Dose 2.
e. 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.
f. Refer to Section 8.3.1 for the time period for collecting SAEs.

1.3.2.1. Phase 2/3 Participants Who Originally Received BNT162b2

After unblinding at Visit 4, participants who originally received BNT162b2 will follow this SoA for their remaining visits.

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

Visit Number	Visit X	Visit Y	Unplanned	Unplanned
Visit Description	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**	**Potential COVID-19/MIS-C Convalescent Visit**
Visit Window (Days)	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**	**28 to 35 Days After Potential COVID-19/MIS-C Illness Visit**
Type of Visit	**Clinic or Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
For participants who are HIV positive, record latest CD4 count and HIV viral load	X	X		
Collect prohibited medication use	X	X	X	X
Obtain anterior nasal swab			X	
Collect blood sample for immunogenicity[b]	~5 mL[c]	~5 mL[c]		~5 mL
Collect AEs as appropriate[d]	X	X	X	X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application		X		
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)			X	X

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

a. Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
b. The participants who are part of the evaluation of persistence of immune response will have blood drawn either at Visit X or Visit Y.
c. If the participants had an unplanned potential COVID-19/MIS-C convalescent visit within ≤42 days before the scheduled visit (Visit X or Visit Y) and if a blood sample was collected as part of the convalescent visit, blood sample collection at the scheduled visit is not required.
d. 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.

1.3.2.2. Phase 2/3 Participants Who Originally Received Placebo

Participants who originally received placebo and accept the offer for receiving BNT162b2 will follow this SoA after unblinding at Visit 4 (in Section 1.3.2).

An unplanned potential COVID-19/MIS-C illness visit and unplanned potential COVID-19/MIS-C convalescent visit are 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.

Visit Number	A	B	C	D	E	F	Unplanned	Unplanned
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**	**Potential COVID-19/MIS-C Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Dose 2**	**19 to 23 Days After Visit A**	**28 to 35 Days After Visit B**	**175 to 189 Days After Visit B**	**350 to 378 Days After Visit B**	**532 to 560 Days After Visit B**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Telephone**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
Confirm participant originally received placebo	X							
Measure vital signs (including body temperature)	X	X						
Perform targeted physical examination	X	X						
For participants who are HIV positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect prohibited medication use	X	X	X	X	X	X	X	X

Visit Number	A	B	C	D	E	F	Unplanned	Unplanned
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**	**Potential COVID-19/MIS-C Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Dose 2**	**19 to 23 Days After Visit A**	**28 to 35 Days After Visit B**	**175 to 189 Days After Visit B**	**350 to 378 Days After Visit B**	**532 to 560 Days After Visit B**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Telephone**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
Obtain anterior nasal swab	X	X					X	
Collect blood sample for immunogenicity								~5 mL
Review temporary delay criteria	X	X						
Confirm continued eligibility	X	X						
Obtain vaccine vial allocation via IRT	X							
Administer BNT162b2	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Collect AEs as appropriate[b]	X	X	X				X	X
Collect SAEs as appropriate[c]	X	X	X	X			X	X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application						X		

Visit Number	A	B	C	D	E	F	Unplanned	Unplanned
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**	**Potential COVID-19/MIS-C Convalescent Visit**
Visit Window (Days)	**175 to 189 Days After Dose 2**	**19 to 23 Days After Visit A**	**28 to 35 Days After Visit B**	**175 to 189 Days After Visit B**	**350 to 378 Days After Visit B**	**532 to 560 Days After Visit B**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Type of Visit	**Clinic**	**Clinic**	**Telephone**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**	**Clinic**
Collection of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: CRF = case report form; HIV = human immunodeficiency virus; IRT = interactive response technology; MIS-C = multisystem inflammatory syndrome in children.

a. Potential MIS-C visit: hospitalization for a severe illness with no other alternative etiology.
b. 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.
c. 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 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. 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.

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.[1,2]

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.[3,4]

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.[5] 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.[6] 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.[7,8,9] Nevertheless, severe cases, including those requiring intensive care support, have been reported.[3] Of US children diagnosed with COVID-19, 5.7% to 20% were hospitalized, including 0.58% to 2.0% admitted to an ICU.[10]

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.[4,11] MIS-C is a febrile hyperinflammatory condition with frequent evidence of cardiac damage and dermatologic, mucocutaneous, and GI features.[11] The syndrome appears to have some overlap with Kawasaki disease shock syndrome.[12,13] 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.[14] As of 29 June 2020, approximately 1000 cases

have been reported.[14] 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%).[15] Death rates of 2% to 4% have been reported.[14] MIS-C has been reported in many countries throughout North America, Europe, Asia, and Latin America,[16] including the US,[4,11] Italy,[17] and France.[18] The United States currently has the most reported cases globally, with the number of confirmed cases continuing to rise globally. There are currently no licensed vaccines or effective antiviral drugs to prevent SARS-CoV-2 infections or the disease it causes, COVID-19.[19]

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 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. VE from Phase 2/3 for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95%, with 8 COVID-19 cases in the active vaccine group compared to 162 COVID-19 cases in the placebo 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.

This Phase 1/2/3 study (C4591007) will evaluate up to 3 different dose levels of BNT162b2 in children for safety, tolerability, immunogenicity, and efficacy depending on accrual of a

sufficient number of cases. Phase 1 includes the dose-finding portion of the study based on the acceptable blinded safety data in 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 this study will be selected based on the Phase 1 safety, tolerability, and immunogenicity data. Phase 2/3 includes the noninferiority comparison of immune responses in participants ≥5 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 accrual of a sufficient number of cases) will also be evaluated in Phase 2/3 of this study.

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 study[23] 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.[24] Vaccine-related enhanced disease for vaccines against related coronaviruses (SARS-CoV-1 and MERS) has been reported only in animal models.[25,26] 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]

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 through 17 years of age were enrolled in the Phase 3 trial, safety data for this age group are limited. However, available data are consistent with the safety profile in the adult population, and it is biologically reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 through 17 years. The potential risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. 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.[22]

In order for the study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV is permitted in Phase 2/3. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, or HBV infections are less likely to be at increased safety risk as a participant in this vaccine study than individuals with other chronic stable medical conditions.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162b2 RNA-based COVID-19 vaccine may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [BNT162b2 RNA-Based COVID-19 Vaccine]		
Potential for greater local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination as compared to adults/adolescents in the C4591001 study.	These are common adverse reactions seen with other vaccines, as noted in the FDA CBER guidelines on toxicity grading scales for healthy adult and adolescent volunteers in preventive vaccine clinical trials.[27] The most common events reported in C4591001 were mild to moderate pain at the injection site, fatigue, and headache.[22]	To address reactogenicity concerns, dose finding has been included as outlined. In addition, 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.
Unknown AEs with a novel vaccine in children ≥5 to <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.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with RSV, feline coronavirus, and Dengue virus vaccines.	No evidence of disease enhancement has been reported in the C4591001 study to date.[24] Temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 neutralizing titers.
MIS-C.	Febrile hyperinflammatory condition with multisystem (≥2) organ involvement as defined in Section 8.1.	MIS-C will be prospectively collected as a potential for COVID-19/MIS-C illness visits for the duration of study participation.

Potential 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. To minimize the total amount of blood drawn, all participants in Phase 1 and participants contributing to the immunogenicity analysis in Phase 2/3 will have at most 3 planned blood draws, with all remaining participants having 2 planned blood draws.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

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

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures 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

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 participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162b2 at each dose level	In participants complying with the key protocol criteria (evaluable participants): At baseline, before Dose 2, and 7 days after Dose 2, • GMTs at each time point • GMFR from before Dose 1 (baseline) to each subsequent time point after vaccination	• 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		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• 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 at the selected dose level in the first approximately 450 participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, from each vaccine group, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 1 month after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 at the selected dose level in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention from each vaccine group, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To demonstrate the noninferiority of the immune response elicited by prophylactic BNT162b2 at the selected dose level in Phase 2/3 participants without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection: • 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	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: • 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	• SARS-CoV-2 neutralizing titers

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
Secondary Immunogenicity/Efficacy:	**Secondary Immunogenicity/Efficacy:**	**Secondary Immunogenicity/Efficacy:**
To describe the immune responses elicited by prophylactic BNT162b2 at selected dose level and persistence of immune response 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 group: At baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers
If at least 22 cases are accrued: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants 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: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up
If at least 22 cases are accrued: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants 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: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants without evidence of past SARS-CoV-2 infection	In evaluable participants without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
Exploratory:	**Exploratory:**	**Exploratory:**
To evaluate the immune response over time to prophylactic BNT162b2 at selected dose level and persistence of immune response 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: At baseline and at 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in Phase 2/3 participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe COVID-19 and severe COVID-19 cases in all participants with and without serological or virological evidence of past SARS-CoV-2 infection		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• Confirmed cases as per CDC criteria
To describe the serological responses in Phase 2/3 participants, to BNT162b2 at the selected dose level in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 neutralizing titers
To describe the safety and immunogenicity of prophylactic BNT162b2 at the selected dose level in children with stable HIV disease		• All safety and immunogenicity endpoints described above will be analyzed descriptively

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2/3 study in healthy children ≥5 to <12 years of age.

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.

4.1.1. Phase 1

Phase 1 is the open-label dose-finding portion of the study to evaluate safety, tolerability, and immunogenicity of BNT162b2 administered on a 2-dose (separated by approximately 21 days) schedule. Dose finding is being initiated in this study 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.

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 the Phase 2/3.

4.1.2. Phase 2/3

Phase 2/3 will evaluate safety, tolerability, immunogenicity, and efficacy (depending on accrual of a sufficient number of cases) of the selected dose level from Phase 1. All participants will have blood drawn at baseline prior to Dose 1 and 6 months after Dose 2. The noninferiority comparison to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and at 1, 6, 12 (original BNT162b2 group only), and 24 months after Dose 2 (original BNT162b2 group only). In addition, efficacy against confirmed COVID-19 and against asymptomatic infection will also be assessed. Efficacy will only be assessed if at least 22 cases are accrued.

At a 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.

4.1.3. Number of Participants

4.1.3.1. Phase 1: Open-Label Dose Finding

This open-label dose-finding phase will consist of up to 3 different dose levels, with 16 participants per dose level, with a total of 48 participants; Table 1.

Table 1. Phase 1 Participants

Total	Up to 3 Dose Levels of BNT162b2	Active	Placebo
48	16/16/16	16	N/A

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

Phase 2/3 will evaluate the safety, tolerability, immunogenicity, and efficacy (depending on accrual of a sufficient number of cases) of the selected dose level from Phase 1, with a total of approximately 2250 participants. Participants will be randomized in a 2:1 ratio to receive active vaccine or placebo (Table 2).

The first approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) randomized in this phase will contribute to the noninferiority comparison at 1 month after Dose 2 and will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2. For the persistence time points of 12 and 24 months after Dose 2, approximately 70 participants in the original BNT162b2 group will have an immunogenicity blood draw in order to contribute to the analysis. All approximately 2250 participants will contribute to the VE analysis for conditional VE and asymptomatic infection. Efficacy will only be assessed if at least 22 cases are accrued.

Table 2. Phase 2/3 Participants – Blood Draws for Immunogenicity/Efficacy Analyses

	Total	Active	Placebo
Baseline blood draw	2250	1500	750
1 Month after Dose 2	450	300	150
6 Months after Dose 2	2250	1500	750
12 Months after Dose 2	70	70	N/A
24 Months after Dose 2	70	70	N/A

All participants will contribute to the safety, tolerability, and efficacy assessments (Table 3).

Table 3. Phase 2/3 Participants – Safety and Tolerability/Efficacy Assessments

Total	Active	Placebo
2250	1500	750

4.1.4. Intervention Groups and Duration

Phase 1: Dose finding will begin at the low-dose level. Dosing will commence at the mid-dose level upon confirmation of acceptable safety assessment at the low-dose level after Dose 1. The same process will be followed when moving to the high-dose level.

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. 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.

Phase 2/3: To proceed to the Phase 2/3 evaluation, safety, tolerability, immunogenicity, and efficacy (depending on accrual of a sufficient number of cases) data from 7 days after Dose 2 for the selected vaccine dose level from Phase 1 will be confirmed to be acceptable.

Duration: Participants are expected to participate for up to a maximum of approximately 26 months.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19/MIS-C illness visit and subsequent convalescent visit will occur. As part of these visits, samples (anterior nasal swab and blood [convalescent visit]) will be taken for antigen and antibody assessment as well as recording of COVID-19/MIS-C–related clinical and laboratory information (including local diagnosis).

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

Based on acceptable blinded safety data in the group of 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. Therefore, this study will start with a 10-µg dose level for Phase 1 participants, which was well tolerated in adults 18 to 55 years of age in C4591001, before moving to a higher dose level.

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. 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 ≥5 to <12 years of age, at the time of randomization, at Visit 1.

    - 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'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'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. **Phase 1 only:** Receipt of medications intended to prevent COVID-19/MIS-C.

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

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

6. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

7. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus.

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

9. Female who is pregnant or breastfeeding.

Prior/Concomitant Therapy:

10. Previous vaccination with any coronavirus vaccine.

11. 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.

12. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments:

Not applicable.

Other Exclusions:

15. 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's parent(s)/legal guardian 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 ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness (for Phase 1, confirmed COVID-19 infection is an exclusion criterion):

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

- New loss of taste/smell;
- Sore throat;
- Nausea;
- Abdominal pain

2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy 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.

Phase 1 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 Phase 2/3.
The investigational RNA vaccine candidate and saline placebo, in Phase 2/3, 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.
- Normal saline (0.9% sodium chloride solution for injection).

6.1. Study Intervention(s) Administered

Intervention Name	BNT162b2 (BNT162 RNA-LNP Vaccine Utilizing modRNA)	Saline Placebo
Type	Vaccine	Placebo
Dose Formulation	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10 µg, 20 µg, or 30 µg, with an option for 3 µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement.	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 (Visits 1 and 2, and Visit A and Visit B for Phase 2/3 participants who go on to receive BNT162b2) 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.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. 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, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/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.

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 Doses 1 and 2 in Phase 2/3) 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 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.

At Visit 4 (6 months after Dose 2), to allow administration of BNT162b2 to participants who originally received placebo, site staff will be unblinded to an individual participant's original vaccine allocation.

6.3.3. Blinding of the Sponsor

For the Phase 1 in which only active vaccine is being administered, blinding is not applicable to the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation for Doses 1 and 2 in Phase 2/3. All laboratory personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study in Phase 2/3. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (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. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team.

- At Visit 4, when a participant who originally received placebo receives BNT162b2 per the SoA in Section 1.3.2.2, 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 Phase 2/3 up to Visit 4, 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 Visit 4 will be provided separately.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant 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 (see Section 7).

Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal or pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

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 Visit 3.

Receipt of blood/plasma products or immunoglobulins is prohibited within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine or investigational 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.

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, name of the medication, dose, unit, route, and frequency) 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 for Phase 1 participants and Visit 4 for Phase 2/3 participants).
- Details of any blood/plasma products, immunoglobulins (eg, IVIG), or immunomodulators (eg, anakinra, tocilizumab) during study participation.
- Antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, exoparin, warfarin).
- Any prescribed medication to treat potential COVID-19 or MIS-C illness cases.

6.6. 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 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.

- The participant's parent(s)/legal guardian 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).

6.7. 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 8.15).

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.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant's parent(s)/legal guardian. All attempts to contact the 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'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'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'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's parent(s)/legal guardian specifically withdraws consent for any further contact with persons previously authorized to provide this information. The 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'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's parent(s)/legal guardian and reschedule the missed visit as soon as possible and counsel the participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule and ascertain whether or not the 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'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'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 in this study is approximately 15 mL for Phase 1 and Phase 2/3 participants who will contribute to immunogenicity assessments. The remaining Phase 2/3 participants will have a 10-mL blood draw. Additionally, 5 mL of blood will be taken at an unplanned convalescent visit at any time a participant develops symptoms indicating a potential COVID-19/MIS-C infection. **Note**: If the participants had an unplanned potential COVID-19/MIS-C convalescent visit within ≤42 days before the scheduled visit (Visit 5 or 6) and if a blood sample was collected as part of the convalescent visit, blood sample collection at the scheduled visit is not required.

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 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.[28] 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; 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;
- Vomiting.

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 pain[10]

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): ≥34 in 5- to 6-year age group, >30 in ≥6- to 13-year age group;
  - HR (beats/min): >140 in 5- to 10-year age group, >100 in ≥10-year age group;
  - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg[29];
- Respiratory failure (defined as needing high-flow oxygen, including CPaP/BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg):
    - <70 + (age in years × 2) for age up to 10 years, <90 + (age in years × 2) 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 baseline[29];
- Admission to an ICU;
- Death.

Confirmed MIS-C definition:[30] as per the CDC MIS-C case definition:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, acute kidney injury);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
    - Dermatologic (eg, rash, mucocutaneous lesions);
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR
- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

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

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result;

- Current or recent exposure is established by SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms;

- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

8.1.1. 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.

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'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 brief targeted physical examination will include, at a minimum, measurement of height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

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

8.2.2. Vital Signs

Temperature, pulse rate, RR, and BP will be assessed.

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's parent(s)/legal guardian will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the personal device of the participant's parent(s)/legal guardian. At the time of randomization, all 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 and Dose 2). 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.

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.

8.2.4.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials.[27]

8.2.4.2. Local Reactions

During the reactogenicity e-diary reporting period, participants' parents/legal guardians will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary 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'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 for pediatric caliper device) for the first 7 days following vaccination (Days 1 through 7), and then categorized as mild, moderate, or severe using the scale shown in in Table 4. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 4.

If redness or swelling >14 caliper units 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 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 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe[a] (Grade 3)[a]	Potentially Life Threatening (Grade 4)[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain (tenderness) at the injection site
Redness	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
Swelling	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

a. Parent(s)/legal guardians of the participants experiencing local reactions >14 caliper units (>7 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

During the reactogenicity e-diary reporting period, the 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's parent(s)/legal guardian as absent, mild, moderate, or severe according to the grading scale in Table 5.

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

Table 5. Systemic Event Grading Scale

	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
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.

8.2.4.4. Fever

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

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a

participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 6. Scale for Fever

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

8.2.4.5. 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 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, 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 the impacted vaccine candidate for all dose levels.
- 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 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°C (>104.0°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 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'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'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 participants' 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

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 2
(Phase 1 – Visit 4; Phase 2/3 – Visit 3). In addition, any AEs occurring up to 48 hours after each subsequent blood draw and nasal swab collection must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent through 6 months after Dose 2 (Phase 1 – Visit 5; Phase 2/3 – Visit 4).

Phase 2/3 Participants Who Originally Received Placebo:

At Visit 4, all participants will be unblinded and if they originally received placebo will be offered BNT162b2. For participants who originally received placebo and go on to receive BNT162b2 as Dose 3 and Dose 4, the time period for actively eliciting and collecting AEs and SAEs will continue from the receipt of BNT162b2 (Dose 3 and Dose 4), through and including 1 month after Dose 4 (Visit C). SAEs will be collected from the time of receipt of BNT162b2 (Dose 3 and Dose 4) through approximately 6 months after Dose 4 of BNT162b2 (Visit D).

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 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: 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.

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 as per the time period for actively collecting AEs and SAEs (after the start of study intervention and until 6 months 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

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

Not applicable.

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

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 or 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/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.
- Measure the participant's vital signs (including body temperature).
- On the day of and before vaccination, perform 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.
- If appropriate, discuss contraceptive use as described in Section 5.3.1.
- Record nonstudy vaccinations as described in Section 6.5.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.

- Obtain a nasal (anterior nares) swab (collected by site staff) and provide instructions to the participant's parent(s)/legal guardian on the technique for collecting a nasal swab at home.

- Collect a blood sample (approximately 5 mL) for immunogenicity.

- 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.

- 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 8.14), 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 8.14 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°C (≥102.1°F).
- Redness or swelling at the injection site >14 caliper units (or >7 cm).
- Grade 3 pain 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'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.
- Measure the participant's vital signs (including body temperature).

- On the day of and before vaccination, perform 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.

- 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).

- 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.

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

- Collect a blood sample (approximately 5 mL) for immunogenicity testing.

- 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.

- 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/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°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 14 caliper units (or >7 cm).
  - Grade 3 pain 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/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.
- 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/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 6 – 12-Month Follow-up Visit (350 to 378 Days After Visit 2)

- Contact the participant's parent(s)/legal guardian by telephone.
- 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 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.

8.11.1.7. Visit 7 – 24-Month Follow-up Visit (714 to 742 Days After Visit 2)

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.

- 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

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.

- Obtain the participant's medical history of clinically significance.

- Measure the participant's vital signs (including body temperature).

- On the day of and before vaccination, perform physical examination including at a minimum, measurement of height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

- 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.

- 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.

- Discuss contraceptive use as described in Section 5.3.1.

- Record nonstudy vaccinations as described in Section 6.5.

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

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

- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.

- 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.

- Collect a blood sample (approximately 5 mL) for immunogenicity testing.

- 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.

- 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 8.14), 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 8.14 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 ≥39.0°C (≥102.1°F).

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

    - Grade 3 pain 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/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.

- 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.

- 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).

- Measure the participant's vital signs (including body temperature).

- On the day of and before vaccination, perform physical examination including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

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

- 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 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.

- 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°C (≥102.1°F).

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

    - Grade 3 pain 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-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.

- 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/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 since Visit 1 (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.

- 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.

8.11.2.4. Visit 4 – 6-Month Follow-up Visit (175 to 189 Days After Visit 2)

- 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 since Visit 3 (if any).

- Collect a blood sample (approximately 5 mL) for immunogenicity testing.

- 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, complete this visit for the remainder of visit activities and schedule an appointment for the participant for the next study visit as in Section 8.11.3.

    - If the participant originally received placebo, move the participant to Section 8.11.4 for the remainder of this visit's activities and future 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.

- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3. Phase 2/3 Participants Who Originally Received BNT162b2

8.11.3.1. Visit X – 12-Month Follow-up Visit (350 to 378 Days After Visit 2)

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 since Visit 4 (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: If the participant had an unplanned potential COVID-19 convalescent visit within ≤42 days prior to this visit, blood collection is not required at this visit.

- 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.

- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.3.2. Visit Y – 24-Month Follow-up Visit (714 to 742 Days After Visit 2)

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 since Visit X (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: If the participant had an unplanned potential COVID-19 convalescent visit within ≤42 days prior to this visit, blood collection is not required at this visit.

- 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.

- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

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

8.11.4. Phase 2/3 Participants Who Originally Received Placebo

8.11.4.1. Visit A – Dose 3 (175 to 189 Days After Dose 2 and Same Date as Visit 4)

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 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.

- Measure the participant's vital signs (including body temperature).

- On the day of and before vaccination, perform physical examination including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

- 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.

- 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.

- If appropriate, discuss contraceptive use as described in Section 5.3.1.
- 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 that the participant meets none of the temporary delay criteria as described in Section 5.5.
- 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.
- 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. 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/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.

- 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.

- If appropriate, discuss contraceptive use as described in Section 5.3.1.

- 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).

- Measure the participant's vital signs (including body temperature).

- On the day of and before vaccination, perform physical examination including, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.

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

- 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 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.

- 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/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 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 since Visit 1 (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 – 6-Month Follow-up Telephone Contact (After Dose 4) (175 to 189 Days After Visit B)

- 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 since Visit 3 (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 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 – 12-Month Follow-up Telephone Contact (After Dose 4) (350 to 378 Days After Visit B)

- Contact the participant's parent(s)/legal guardian by telephone.
- 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 since Visit 4 (if any).
- 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 – 18-Month Follow-up Telephone Contact (After Dose 4) (532 to 560 Days After Visit B)

This visit can be performed as a telephone visit.

- 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 since Visit E (if any).
- 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.

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

If a participant's parent/legal guardian reports redness or swelling >14 caliper units 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'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 (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 (All Participants)

COVID-19 Surveillance: If a participant experiences 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 the symptom(s) has an identifiable alternative etiology, is clinically insignificant, or is a single symptom lasting 1 calendar day. 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

The participant's parent(s)/legal guardian may utilize a COVID-19/MIS-C illness e-diary through an application (see Section 8.14) 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;
- Hospitalization for a severe illness with no other alternative etiology

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.

- 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): ≥34 in 5- to 6-year age group, >30 in ≥6- to 13-year age group;

        - HR (beats/min): >140 in 5- to 10-year age group; >100 in ≥10-year age group;

        - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg)[29];

    - Respiratory failure (defined as needing high-flow oxygen, including nasal CPaP/BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);

    - Evidence of shock or cardiac failure:

        - SBP (mm Hg) <70 + (age in years × 2) for age up to 10 years, <90 + (age in years × 2) 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 baseline[29];
- 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.

- Schedule an appointment for the participant to return for the potential COVID-19/MIS-C convalescent visit.
- 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)

- Record AE/SAEs as appropriate, as described in Section 8.3. Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured to describe disease endpoints for lack-of-efficacy assessment 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.

- Collect a blood sample (approximately 5 mL) for immunogenicity testing.

- Collect/update COVID-19–related clinical and laboratory information (detailed in Section 8.13.1).

- 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.

8.14. 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'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's parent(s)/legal guardian and the study site staff will be established. The 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'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'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's parent(s)/legal guardian to ascertain the reason and also to obtain details of any missed events.

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

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

- Visits 1, Visit 2, Visit A, and Visit B (Visits A and B per Section 1.3.2.2): 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 Visit 1, Visit 2, Visit A, and Visit B 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:

- 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.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. 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 × 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 evaluate noninferiority of the immune response to prophylactic BNT162b2 at the selected dose level in participants ≥5 to <12 years of age at 1 month after Dose 2 compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. The evaluable immunogenicity population will be used for the following hypothesis testing:

H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, $\ln(\mu_2)$ and $\ln(\mu_1)$ are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients ≥5 to <12 years of age, and 16 to 25 years of age from Phase 2/3 of the C4591001 study, respectively, measured 1 month after Dose 2.

Noninferiority will be declared if the lower limit of the 95% CI for the GMR (≥5- to <12-year age group to the 16- to 25-year age group from C4591001) is >0.67.

9.1.2.2. Statistical Hypothesis Evaluation for Efficacy

The secondary efficacy endpoints are to evaluate VE, which is defined as VE = 100 × (1 – IRR). 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. VE_1

represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior infection, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination. The assessment of VE will be based on testing the following hypothesis:

$$H_0: VE \leq 20\% \text{ vs } H_1: VE > 20\%$$

for VE_1 and VE_2 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

The primary immunogenicity objective of noninferiority will be evaluated first. If the primary objective is met and the required number of confirmed COVID-19 cases is accrued, the secondary VE objectives, VE_1 and VE_2, will be tested sequentially in the order as stated. Thus, type I error is controlled to the desired level of 2.5%.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 16 participants receiving active vaccine per group for each dose level; 3 groups are studied, corresponding to a total of 48 participants.

Phase 2/3 will comprise approximately 2250 participants (randomization ratio of 2:1 so that 1500 receive active vaccine and 750 receive placebo). The total sample size in Phase 2/3 is not based on statistical hypothesis testing.

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 noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants will provide a power of 90.4% to declare the noninferiority of each younger to older age group in terms of neutralizing antibody GMR, 1 month after Dose 2 (see Table 7). Assuming a 25% nonevaluable rate, this will require approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) with 1-month post–Dose 2 blood sample collection in Phase 2/3 of the study to achieve 225 evaluable participants in the active vaccine group.

Table 7. Power Analysis for Noninferiority 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 (≥5- to <12-year 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).

The persistence of immune response will be based on Phase 2/3 participants with baseline and 1-, 6-, 12-, or 24-month post–Dose 2 immunogenicity data. Blood samples will be tested for the first approximately 450 participants at 1 month and 6 months (300 in the active vaccine group, and 150 in the placebo group), and for approximately 70 participants in the original BNT162b2 group at 12 or 24 months after Dose 2. Assuming a nonevaluable rate of 25%, there will be ~225 and ~50 evaluable participants at 1 and 6 months, and later time points, respectively.

Table 8 displays the ratio of the upper 2-sided 95% confidence limit of GMT relative to the GMT as a measure of precision for the immunogenicity endpoint SARS-CoV-2 neutralizing titer. With 50 evaluable participants in the vaccine group, the upper 95% confidence limit of the GMT would be 20% higher than the corresponding GMT.

Table 8. Precision of SARS-CoV-2 Neutralizing Titer GMT

Standard Deviation (Log Value)[a]	Upper 2-Sided 95% Confidence Limit of GMT Relative to GMT × 100	
	50 Evaluable Participants	225 Evaluable Participants
0.65	1.20	1.09

Abbreviation: GMT = geometric mean titer.

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

For VE evaluation, with a total of approximately 2250 participants (1500 participants randomized to the vaccine group and 750 participants randomized to the placebo group), assuming 25% of the participants being nonevaluable and 1.3% annual attack rate, a total of approximately 5 first confirmed COVID-19 illness cases will be observed within 6 months after vaccination. This provides approximately 13.2% power to conclude true VE >20% with assumptions of a true VE of 75%. Dependent 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 22 cases to achieve 70% power, hypothesis testing will be conducted only if at least 22 cases are accrued (Table 9).

Table 9. Power for Vaccine Efficacy Assessment

Power	Total Cases	Case Split[a] to Claim Success[b] (VE%)
13.2%	5	0:5 (100%)
70.7%	**22**	**8:14 (71.4%)**
82.2%	25	10:15 (66.7%)
90.0%	33	14:19 (63.2%)

Abbreviation: VE = vaccine efficacy.

a. Case split numbers represent the number of cases in the active vaccine group vs the number of cases in the placebo group.

b. Success criterion: lower bound of 95% CI for VE >20%.

For safety outcomes, Table 10 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 10. 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=48	N=300	N=1500
0.01%	0.00	0.00	0.03	0.14
0.02%	0.00	0.01	0.06	0.26
0.04%	0.01	0.02	0.11	0.45
0.06%	0.01	0.03	0.16	0.59
0.08%	0.01	0.04	0.21	0.70
0.10%	0.02	0.05	0.26	0.78
0.15%	0.02	0.07	0.36	0.89
0.20%	0.03	0.09	0.45	0.95
0.25%	0.04	0.11	0.53	0.98
0.30%	0.05	0.13	0.59	0.99
0.35%	0.05	0.15	0.65	0.99
0.50%	0.08	0.21	0.78	>0.99
1.00%	0.15	0.38	0.95	>0.99
2.00%	0.28	0.62	>0.99	>0.99
3.00%	0.39	0.77	>0.99	>0.99
5.00%	0.56	0.91	>0.99	>0.99
7.00%	0.69	0.97	>0.99	>0.99
10.00%	0.81	0.99	>0.99	>0.99

Note: N = number of participants in a vaccine group. In Phase 1, 16 participants in each dose level and a total of 48 participants are to be vaccinated with any the 3 dose levels. A total of 1500 participants in Phase 2/3 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	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.
Dose 1 evaluable immunogenicity	Phase 1 only: All eligible randomized participants who receive Dose 1 of the vaccine to which they are randomized, have at least 1 valid and determinate immunogenicity result from the blood sample collected after Dose 1 and before Dose 2, and have no other important protocol deviations before Dose 2 as determined by the clinician.
All-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as 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.
Safety	All randomized 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

CIs 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 ≥5- to <12-year 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	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 will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3. 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 there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are

Endpoint	Statistical Analysis Methods
	those that are neither Tier 1 nor Tier 2 events. Analyses methods are described in Section 9.4.1.1. 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 will be provided for each vaccine group. In addition, for the first approximately 450 participants randomized in Phase 2/3, SAEs from Dose 1 to 1 month after Dose 2 will be summarized using the same method.
Immunogenicity (Phase 2/3)	**GMR of SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years of age to those 16 to 25 years of age in Study C4591001** The GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the ≥5- to <12-year age group to the 16- to 25-year age group 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) of past SARS-CoV-2 infection will be included in the analysis. Noninferiority will be declared if the lower bound of the 2-sided 95% for the GMR is greater than 0.67.

9.4.3. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Immunogenicity (Phase 1)	**GMTs of SARS-CoV-2 neutralizing titers** For SARS-CoV-2 neutralizing titers, GMTs and 2-sided 95% CIs will be provided for each vaccine group at baseline (before Dose 1), before Dose 2, and at 7 days after Dose 2. Statistical methods are described in Section 9.4.1.2.1. **GMFRs of SARS-CoV-2 neutralizing titers** For SARS-CoV-2 neutralizing titers, the GMFRs and 2-sided 95% CIs will be provided for each vaccine group from before Dose 1 to subsequent time points after vaccination (before Dose 2 and 7 days after Dose 2).

Endpoint	Statistical Analysis Methods
	GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The statistical methods are described in Section 9.4.1.2.2.
Immunogenicity (Phase 2/3)	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 is determined as a COVID-19 case or has a positive N-binding result.
VE (Phase 2/3)	**Ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of 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** VE will be estimated by 100 × (1 - 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. 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. **Ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of 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** The same analysis method used for the first VE endpoint will be applied. **Ratio of incidence of asymptomatic infection of SARS-CoV-2 in participants for the active vaccine group to the placebo group in evaluable participants without evidence of past SARS-CoV-2 infection** VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method. The analysis will be based on the evaluable efficacy population and the all-available efficacy population without serological or virological

Endpoint	Statistical Analysis Methods
	evidence of past SARS-CoV-2 infection. Missing efficacy data will not be imputed.

9.4.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
Safety	Descriptive summary of all safety endpoints will be provided for children with stable HIV disease.
Immunogenicity (Phase 2/3)	GMTs and GMFRs of SARS-CoV-2 neutralizing titers 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. In each subset of participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19, GMTs/GMCs and GMFRs of SARS-CoV-2 neutralizing titers will be summarized using the same statistical analysis method described for the secondary immunogenicity endpoints. Empirical RCDCs 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	Counts, percentages, and the associated Clopper-Pearson 95% CIs of confirmed COVID-19, confirmed severe COVID-19, and confirmed MIS-C cases will 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:

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

- Safety data through 1 month after Dose 2 from the first approximately 450 participants randomized in Phase 2/3.

- Immunogenicity data through 1 month after Dose 2 from the first approximately 450 participants randomized in Phase 2/3 (noninferiority comparison of SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years of age compared to those in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study).

- Safety data through 1 month after Dose 2 from all participants in Phase 2/3.

- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.

- Complete safety, persistence-of-immunogenicity, and efficacy analysis after complete data are available or at the end of the study.

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

- 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 to proceed

    - Select dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the 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 may not be started

    - Whether any dose level may be terminated early

- 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 his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant 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's parent(s)/legal guardian 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's parent(s)/legal guardian.

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

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about his or her right to access and correct his or her child's personal data and to withdraw consent for the processing of 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.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

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

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

- 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 Meeting the AE Definition

- 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:
  - 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.

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.

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.

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 Report Form
• Facsimile transmission of the Vaccine SAE Report 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 Report 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 Report Form pages within the designated reporting time frames.

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;
    - Injectable.

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected 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
ALT	alanine aminotransferase
app	application
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransferase
BiPaP	bilevel positive airway pressure
BNP	brain natriuretic peptide
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	creatine 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
EU	European Union
EUA	emergency use authorization

Abbreviation	Term
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
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle

Abbreviation	Term
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
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
PPE	personal protective equipment
PT	prothrombin time
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
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
ULN	upper limit of normal
US	United States
VE	vaccine efficacy
VAED	vaccine-associated enhanced disease
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/mm^3 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

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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 AND YOUNG ADULTS

Study Sponsor	BioNTech
Study Conducted By	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccine
US IND Number:	19736
EudraCT Number:	2020-005442-42
Protocol Number:	C4591007
Phase:	1/2/3

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 and Young Adults

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 4	29 Sep 2021	• Revised the success criterion for the efficacy hypotheses to the lower limit of 95% CI >30, in response to regulatory feedback. • Added Section 5.3.2, 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	• 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. • Revised an objective and corresponding endpoints 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	• Made the following updates in response to commitments made to CBER concerning myocarditis and pericarditis:
		  • 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.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• 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	• 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. • 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: • 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.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**

		• 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:
		  • 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:
		  • 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.

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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 and Young Adults.

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.

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. With the robust immune responses elicited in adolescents to minimize reactogenicity and risk of other AEs and to potentially unify the dose levels across children and young adults, additional lower dose levels of BNT162b2 (3 µg, 10 µg) will be evaluated to determine whether similar immune responses are elicited. For this lower-dose evaluation portion, a new cohort of Phase 1 participants will be enrolled in 3 age groups: >5 to <12, 12 to <16, and 16 to <30 years of age to assess safety, tolerability, and immunogenicity. The Phase 2/3 BNT162b2 dose level 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). 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.

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 <30 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, Lower-Dose Evaluations, and Obtaining Serum Samples for Potential Troponin I Testing

Phase 1 Open-Label Dose-Finding Evaluation						
	≥6 Months to <2 Years	**≥2 to <5 Years**	**≥5 to <12 Years**	**12 to <16 Years**	**16 to <30 Years**	**Total**
Dose level	3 µg	3/10 µg	10/20/30 µg			
Participants	16[a]	16/32[a]	16/16/16[b]			112
Phase 2/3 Observer-Blinded, Placebo-Controlled Selected-Dose Evaluation						
Dose level	3 µg	3 µg	10 µg			
Participants	2250 (active 1500; placebo 750)	2250 (active 1500; placebo 750)	4500 (active 3000; placebo 1500)			9000
Phase 1 Open-Label Lower-Dose Evaluation						
Planned dose level(s)			3 µg	3/10 µg[c]	3/10 µg[c]	
Participants			32	32/32	32/32	160
Phase 2/3 Open-Label Lower-Dose Evaluation						
Planned dose level			TBD	TBD	TBD	
Participants			300	300	300	900
Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing						
Planned dose level			10 µg	30 µg		
Participants			750 (active 500; placebo 250)	500 (active 500; placebo 0)		1250

a. Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
b. 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.
c. Both dose levels will start concurrently.

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.

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.

Lower-dose evaluation: Is the open-label lower-dose evaluation portion of the study that will evaluate safety, tolerability, and immunogenicity of BNT162b2 on a 2-dose (separated by approximately 21 days) schedule in up to 3 age groups (participants ≥5 to <12 years, 12 to <16 years, and 16 to <30 years of age).

The purpose of the Phase 1 lower-dose evaluation is to evaluate safety and immunogenicity of BNT162b2 from up to 2 different dose levels in each age group.

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 the Phase 2/3 lower-dose evaluation portion of the study.

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 and 6 months after Dose 2. Immunobridging to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and at 1, 6, 12 (original BNT162b2 group only), and 24 months after Dose 2 (original BNT162b2 group only). In addition, efficacy against confirmed COVID-19 and against asymptomatic 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. 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. 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 have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study.

Lower-dose evaluation: 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 lower-dose evaluation.

In this open-label study, all participants will have blood drawn at baseline prior to Dose 1 and at 1 and 6 months after Dose 2. Immunobridging to comparator participants in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and 1 and 6 months after Dose 2.

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 µg or placebo, and 500 participants 12 to <16 years of age: open-label receipt of BNT162b2 30 µg.

Number of Participants

Phase 1: Open-Label Dose-Finding and Lower-Dose Evaluation

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 and a minimum of 32 participants per dose level (total of 160 participants) for the lower-dose 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 1 Lower-Dose Evaluation Participants				
Age Group	**Total**	**Up to 2 Dose Levels of BNT162b2[a]**	**Active**	**Placebo**
≥5 to <12 Years	32	32	32	N/A
12 to <16 Years	64	32/32	32	N/A
16 to <30 Years	64	32/32	32	N/A

a. A dose level may be expanded to enroll more than 32 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 9000 participants, as an additional 2250 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 will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure this subset is representative of the whole study.

For the persistence time points of 12 and 24 months after Dose 2, approximately 70 participants from each age group in the original BNT162b2 vaccine group will have an immunogenicity blood draw in order to contribute to the analysis. All approximately 9000 participants will contribute to the VE analysis for conditional VE. Approximately 4500 participants who had post–Dose 1 blood sample collection will contribute to the asymptomatic infection analysis. 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.

Phase 2/3 Selected-Dose Participants – 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	9000	6000	3000	4500	3000	1500	2250	1500	750
1 Month after Dose 2	1350	900	450	450	300	150	450	300	150
6 Months after Dose 2	4500	3000	1500	2250	1500	750	1125	750	375
12 Months after Dose 2	210	210	N/A	70	70	N/A	70	70	N/A
24 Months after Dose 2	210	210	N/A	70	70	N/A	70	70	N/A

a. Number of participants shown is for each of these 2 younger age groups.

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	2250	1500	750
≥6 Months to <2 Years	2250	1500	750
All age groups	9000	6000	3000

Lower-dose evaluation: Is the open-label 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 lower-dose evaluation, with a total of approximately 900 active participants.

Approximately 300 active participants in each age group in this phase will contribute to the immunobridging analysis at 1 month after Dose 2 and the overall analysis of the persistence of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure this subset is representative of the whole study.

Phase 2/3 Lower-Dose Evaluation Participants – Blood Draws for Immunogenicity/Efficacy Assessments				
	All Age Groups		⩾5 to <12, 12 to <16 Years, and 16 to <30 Years of Age[a]	
	Total	Active	Active	Placebo
Baseline blood draw	900	900	300	N/A
1 Month after Dose 2	900	900	300	N/A
6 Months after Dose 2	900	900	300	N/A

a. Number of participants shown is for each age group.

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

Phase 2/3 Lower-Dose Evaluation Participants – Safety and Tolerability/Efficacy Assessments		
Total	**Active**	**Placebo**
900	900	N/A

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

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 up to a maximum of approximately 26 months.

Lower-dose evaluation: As higher doses have been assessed in each age group, all age/dose levels will proceed concurrently.

Duration of the lower-dose evaluation portion of the study: Participants are expected to participate for up to a maximum of approximately 6 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: Participants are expected to participate for up to a maximum of approximately 26 months.

Lower-dose evaluation: 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 lower-dose evaluation portion of the study: Participants are expected to participate for up to a maximum of approximately 6 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 6 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 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 ≥ 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 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, and approximately 300 participants enrolled in each age group in the Phase 2/3 lower-dose evaluation portion of the study, will be used for the immunobridging assessment.

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.

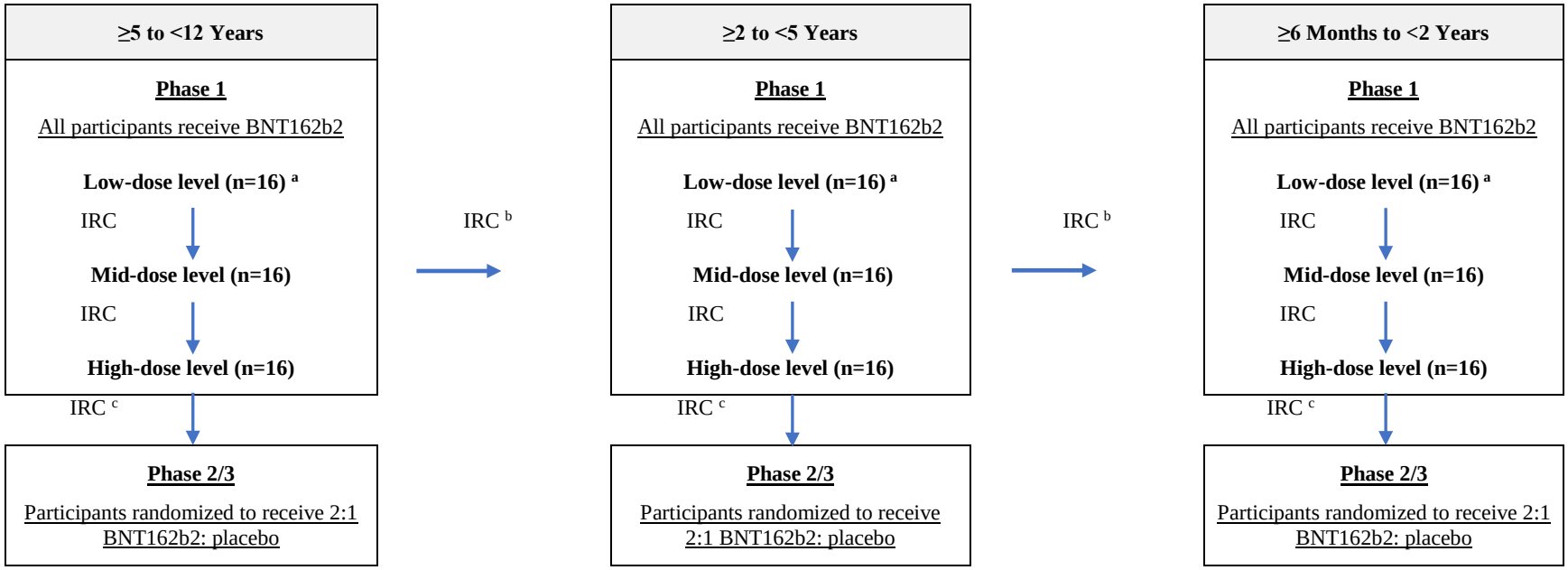
The secondary efficacy objectives are to evaluate VE, defined as 100 × (1 – IRR), against the confirmed COVID-19 illness, in each of the 2 age groups (≥5 to <12 years, and ≥6 months to <2 years and ≥2 to <5 years combined) or across all age groups where immunobridging success is declared in the Phase 2/3 selected-dose portion of the study (if the required number of cases are not accrued in either of the 2 individual age groups). 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. However, if 21 cases are not accrued in either of the 2 age groups (≥5 to <12 years, ≥6 months to <2 years and ≥2 to <5 years combined) where immunobridging success is declared, but 21 cases are accrued across all the age groups where immunobridging success is declared, then hypothesis testing will be conducted across the age groups with immunobridging success.

VE against asymptomatic infection will be evaluated descriptively. VE estimate and 2-sided 95% CI for VE will be provided using the Clopper-Pearson method.

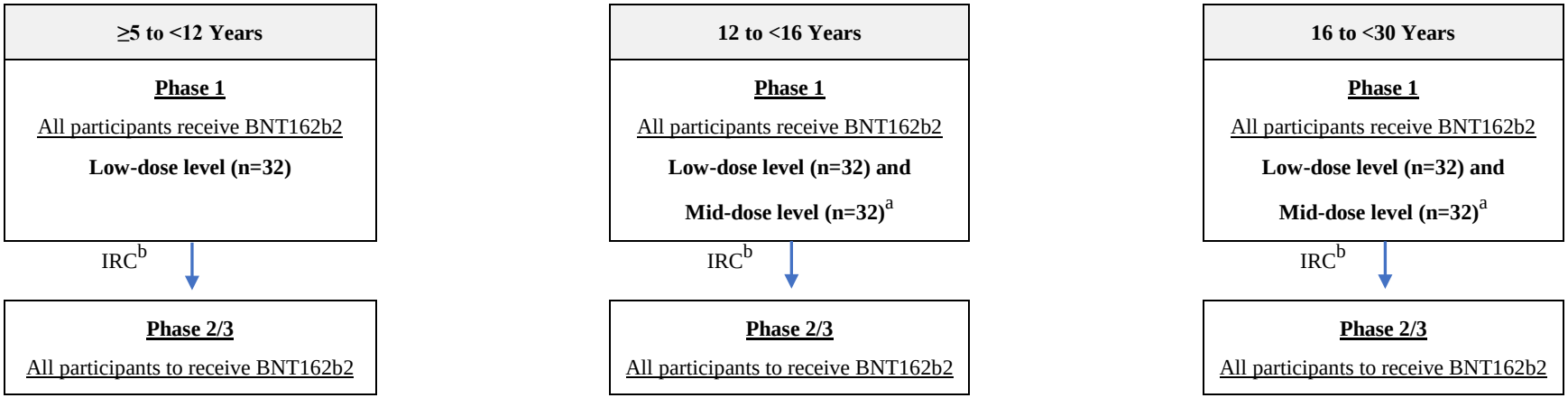
The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine and age group. A 3-tier approach will be used to summarize AEs in the Phase 2/3 selected-dose portion of the study.

1.2. Schema



a. 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.
b. 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.
c. 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.

Phase 1/2/3 Lower-Dose Evaluation



a. Low- and mid-dose levels will start concurrently.
b. 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, Lower-Dose Evaluations, and Obtaining Serum Samples for Potential Troponin I Testing

	≥6 Months to <2 Years	≥2 to <5 Years	≥5 to <12 Years	12 to <16 Years	16 to <30 Years	Total
Phase 1 Open-Label Dose-Finding Evaluation						
Dose level	3 µg	3/10 µg	10/20/30 µg			
Participants	16[a]	16/32[a]	16/16/16[b]			112
Phase 2/3 Observer-Blinded, Placebo-Controlled Selected-Dose Evaluation						
Dose level	3 µg	3 µg	10 µg			
Participants	2250 (active 1500; placebo 750)	2250 (active 1500; placebo 750)	4500 (active 3000; placebo 1500)			9000
Phase 1 Open-Label Lower-Dose Evaluation						
Planned dose level(s)			3 µg	3/10 µg[c]	3/10 µg[c]	
Participants			32	32/32	32/32	160
Phase 2/3 Open-Label Lower-Dose Evaluation						
Planned dose level			TBD	TBD	TBD	
Participants			300	300	300	900
Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing						
Planned dose level			10 µg	30 µg		
Participants			750 (active 500; placebo 250)	500 (active 500; placebo 0)		1250

a. Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
b. 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.
c. Both dose levels will start concurrently.

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.

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**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**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19/ MIS-C Illness Visit[b]**
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**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[c]**	**Telephone**	**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	X							
Confirm use of contraceptives (if appropriate)	X	X	X	X				
Collect nonstudy vaccine information	X	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X	X

Visit Number	1	2	3	4	5	6	7	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**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19/ MIS-C Illness Visit[b]**
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**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[c]**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Measure vital signs (including body temperature)	X	X						
Perform physical examination (including height and weight)[d]	X	X						
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X						
Obtain randomization number and study intervention allocation	X							
Obtain anterior nasal swab	X	X						X
Collect blood sample for immunogenicity	~5 mL	~5 mL	~5 mL					
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X							
Provide a thermometer and caliper (measuring) device	X							
Reactivate reactogenicity e-diary		X						
Ensure the participant's parent(s)/legal guardian/has a caliper device and thermometer		X						

Visit Number	1	2	3	4	5	6	7	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**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19/ MIS-C Illness Visit[b]**
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**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[c]**	**Telephone**	**Telephone**	**Clinic or Telephone**	**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						
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				
Collect AEs[e]	X	X	X	X				X
Collect SAEs[f]	X	X	X	X	X			X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application							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; MIS-C = multisystem inflammatory syndrome in children; SMS = short message service.

a. The visit may be conducted across 2 consecutive days; if so, please refer to Section 8.11.1.1.
b. Potential MIS-C visit: Hospitalization for a severe illness with no other alternative etiology.
c. 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.
d. 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.
e. 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.
f. Refer to Section 8.3.1 for the time period for collecting SAEs.

1.3.2. Phase 1 Lower-Dose Evaluation

Visit Number	101	102	103	104	105
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**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 101**	**6 to 8 Days After Visit 102**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[b]**	**Telephone**
Obtain informed consent and assent (if appropriate)	X				
Assign participant number	X				
Obtain demography and significant medical history data	X				
Confirm use of contraceptives (if appropriate)	X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X	X			
Review temporary delay criteria	X	X			
Measure vital signs (including body temperature)	X	X			
Perform clinical assessment[c]	X	X			
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X			
Obtain randomization number and study intervention allocation	X				
Obtain anterior nasal swab	X	X			
Collect blood sample for immunogenicity[d]	~20 mL/~10 mL/ ~5 mL	~20 mL/~10 mL/ ~5 mL	~20 mL/~10 mL/ ~5 mL		
Administer study intervention	X	X			
Assess acute reactions for at least 30 minutes after study intervention administration	X	X			
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X				
Provide a thermometer and caliper (measuring) device	X				
Reactivate reactogenicity e-diary		X			

Visit Number	101	102	103	104	105
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**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 101**	**6 to 8 Days After Visit 102**	**28 to 35 Days After Visit 102**	**175 to 189 Days After Visit 102**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[b]**	**Telephone**
Ensure the participant or participant's parent(s)/legal guardian has a caliper device and thermometer		X			
Ask the participant or 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			
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	
Collect AEs[e]	X	X	X	X	X
Collect SAEs[f]	X	X	X	X	X
Collect e-diary or assist the participant or participant's parent(s)/legal guardian to delete application					X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; SMS = short message service.

a. The visit may be conducted across 2 consecutive days; if so, please refer to Section 8.11.2.1.
b. 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.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.
e. 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).
f. Refer to Section 8.3.1 for the time period for collecting SAEs.

1.3.3. 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 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. 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 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study. 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 in Section 1.3.3.2 for his or her remaining visits. Participants who originally received BNT162b2 or placebo recipients who decline BNT162b2 will complete the SoA immediately below (Section 1.3.3) before moving to the SoA in Section 1.3.3.1.

Visit Number	1	2	3	4	5	Unplanned
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Week Follow-up Visit[b]**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit[c]**	**Potential COVID-19 Illness/MIS-C Visit[d]**
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**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[e]**	**Clinic**	**Clinic or Telehealth**
Obtain informed consent and assent (if appropriate)	X					
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	
Confirm use of contraceptives (if appropriate)	X	X	X	X		
Collect nonstudy vaccine information	X	X	X	X	X	
Collect prohibited medication use		X	X	X	X	X
Confirm eligibility	X	X				
Review temporary delay criteria	X	X				
Measure vital signs (including body temperature)	X	X				
Perform physical examination (including height and weight)[f]	X	X				
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X				
Obtain randomization number and study intervention allocation	X					
Obtain anterior nasal swab	X	X				X

Visit Number	1	2	3	4	5	Unplanned
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Week Follow-up Visit[b]**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit[c]**	**Potential COVID-19 Illness/MIS-C Visit[d]**
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**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[e]**	**Clinic**	**Clinic or Telehealth**
Collect blood sample for immunogenicity	~5 mL			~5 mL[g]	~5 mL[h]	
Collect blood sample for PBMC isolation[b]	~10 mL		~10 mL		~10 mL	
Administer study intervention	X	X				
Assess acute reactions for at least 30 minutes after study intervention administration	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				
Ensure the participant's parent(s)/legal guardian has a caliper device and thermometer		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				
Review reactogenicity e-diary data (daily review is optimal during the active diary period)	◄——►	◄——►				

Visit Number	1	2	3	4	5	Unplanned
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Week Follow-up Visit[b]**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit[c]**	**Potential COVID-19 Illness/MIS-C Visit[d]**
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**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic or Telephone[e]**	**Clinic**	**Clinic or Telehealth**
Review ongoing reactogenicity e-diary symptoms and obtain stop dates		X		X		
Collect AEs as appropriate[i]	X	X	X	X	X	X
Collect SAEs as appropriate[j]	X	X	X	X	X	X
Unblind the participant and move to either Section 1.3.3.1 or Section 1.3.3.2					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; PBMC = peripheral blood mononuclear cell; SMS = short message service.

a. This visit may be conducted across 2 consecutive dates; if so, please refer to Section 8.11.3.1.
b. Applicable at designated sites only for participants ≥10 years of age whose parent(s)/legal guardian have given consent for this additional blood draw.
c. For Phase 2/3 participants who originally received placebo, it is preferable that Visit 5 and Visit A (Section 1.3.3.2) occur on the same day.
d. Potential MIS-C visit: Hospitalization for a severe illness with no other alternative etiology.
e. 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.
f. 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.
g. Approximately 450 randomized participants in each age group will have blood drawn at 1 month after Dose 2.
h. Not required for the additional 4500 participants included to enlarge the size of the pediatric safety database.
i. 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.
j. Refer to Section 8.3.1 for the time period for collecting SAEs.

1.3.3.1. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

After unblinding at the 6-month follow-up visit, or before if eligible per local or national recommendations, participants who originally received BNT162b2 or placebo recipients who decline BNT162b2 will follow this SoA for their remaining visits, after completing the SoA in Section 1.3.3.

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.

Visit Number	Visit X	Visit Y	Unplanned
Visit Description	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**
Visit Window (Days)	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19/MIS-C Illness Onset**
Type of Visit	**Clinic or Telephone[b]**	**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[c]	~5 mL	~5 mL	
Collect AEs as appropriate[d]	X	X	X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application		X	
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.

a. Potential MIS-C visit: Hospitalization for a severe illness with no other alternative etiology.
b. 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.
c. The participants who are part of the evaluation of persistence of immune response will have blood drawn either at Visit X or Visit Y.
d. 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.

1.3.3.2. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received Placebo

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. 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 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study. 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 in this for his or her remaining visits. Participants who originally received BNT162b2 or placebo recipients who decline BNT162b2 will move to the SoA in Section 1.3.3.1.

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.

Visit Number	A	B	C	D	E	F	Unplanned
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**
Visit Window (Days)	**From Recommendation[b] or 175 to 189 Days After Dose 2**	**19 to 23 Days After Visit A**	**28 to 35 Days After Visit B**	**175 to 189 Days After Visit B**	**350 to 378 Days After Visit B**	**532 to 560 Days After Visit B**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Telephone[c]**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**
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	
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect prohibited medication use	X	X	X	X	X	X	X
Review and consider eligibility	X	X					
Review temporary delay criteria	X	X					
Measure vital signs (including body temperature)	X	X					
Perform physical examination[d]	X	X					
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X					
Obtain anterior nasal swab	X	X					X
Collect blood sample for immunogenicity	X[e]						

Visit Number	A	B	C	D	E	F	Unplanned
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**
Visit Window (Days)	**From Recommendation[b] or 175 to 189 Days After Dose 2**	**19 to 23 Days After Visit A**	**28 to 35 Days After Visit B**	**175 to 189 Days After Visit B**	**350 to 378 Days After Visit B**	**532 to 560 Days After Visit B**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Telephone[c]**	**Telephone**	**Telephone**	**Clinic or Telephone**	**Clinic or Telehealth**
Obtain vaccine vial allocation via IRT	X						
Administer BNT162b2	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Collect AEs as appropriate[f]	X	X	X				X
Collect SAEs as appropriate[g]	X	X	X	X			X
Collect e-diary or assist the participant's parent(s)/legal guardian to delete application						X	

Visit Number	A	B	C	D	E	F	Unplanned
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**18-Month Follow-up Visit**	**Potential COVID-19 Illness/MIS-C Visit[a]**
Visit Window (Days)	**From Recommendation[b] or 175 to 189 Days After Dose 2**	**19 to 23 Days After Visit A**	**28 to 35 Days After Visit B**	**175 to 189 Days After Visit B**	**350 to 378 Days After Visit B**	**532 to 560 Days After Visit B**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
Type of Visit	**Clinic**	**Clinic**	**Telephone[c]**	**Telephone**	**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; HIV = human immunodeficiency virus; IRT = interactive response technology; MIS-C = multisystem inflammatory syndrome in children; SMS = short message service.

a. Potential MIS-C visit: Hospitalization for a severe illness with no other alternative etiology.
b. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
c. 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.
d. A physical examination will include, at a minimum, assessments of general appearance, lungs, cardiovascular system, and lymph node survey.
e. 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.
f. 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.
g. Refer to Section 8.3.1 for the time period for collecting SAEs.

1.3.4. Phase 2/3 Lower-Dose Evaluation

Visit Number	201	202	203	204
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 201**	**28 to 35 Days After Visit 202**	**175 to 189 Days After Visit 202**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Obtain informed consent and assent (if appropriate)	X			
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
Confirm use of contraceptives (if appropriate)	X	X	X	
Collect nonstudy vaccine information	X	X	X	X
Collect prohibited medication use		X	X	X
Confirm eligibility	X	X		
Review temporary delay criteria	X	X		
Measure vital signs (including body temperature)	X	X		
Perform clinical assessment[b]	X	X		
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X		
Obtain randomization number and study intervention allocation	X			
Obtain anterior nasal swab	X	X		
Collect blood sample for immunogenicity[c]	~20 mL/~10 mL/~5 mL		~20 mL/~10 mL/~5 mL	~20 mL/~10 mL/~5 mL
Administer study intervention	X	X		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X		
Explain communication methods (including for e-diary completion), assist with downloading the app, or issue provisioned device, if required	X			

Visit Number	201	202	203	204
Visit Description	**Dose 1[a]**	**Dose 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**
Visit Window (Days)	**Day 1**	**19 to 23 Days After Visit 201**	**28 to 35 Days After Visit 202**	**175 to 189 Days After Visit 202**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Provide thermometer and caliper (measuring) device	X			
Reactivate reactogenicity e-diary		X		
Ensure the participant or participant's parent(s)/legal guardian has a caliper device and thermometer		X		
Ask the participant or participant's parent(s)/legal guardian to complete e-diary and ensure the participant or participant's parent(s)/legal guardian remains comfortable with chosen e-diary platform	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	
Collect AEs as appropriate[d]	X	X	X	X
Collect SAEs as appropriate[e]	X	X	X	X

Abbreviations: AESI = adverse event of special interest; CRF = case report form; HIV = human immunodeficiency virus.

a. This visit may be conducted across 2 consecutive dates; if so, please refer to Section 8.11.6.1.
b. Including, if indicated, a physical examination.
c. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.
d. 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).
e. Refer to Section 8.3.1 for the time period for collecting AESIs/SAEs.

1.3.5. 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 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 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study. 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 in Section 1.3.5.1 for his or her remaining visits. Participants who received BNT162b2 will continue in the study as originally planned.

Visit Number	301	302	303	304	305
Visit Description	**Dose 1[a]**	**Dose 2**	**4-Day Follow-up Visit**	**1-Month Follow-up Visit**	**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**	**175 to 189 Days After Visit 302**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Telephone[b]**	**Telephone**
Obtain informed consent and assent	X				
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
Confirm use of contraceptives (if appropriate)	X	X	X	X	
Collect nonstudy vaccine information	X	X	X	X	X
Collect prohibited medication use		X	X	X	X
Confirm eligibility	X	X			
Review temporary delay criteria	X	X			

Visit Number	301	302	303	304	305
Visit Description	**Dose 1[a]**	**Dose 2**	**4-Day Follow-up Visit**	**1-Month Follow-up Visit**	**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**	**175 to 189 Days After Visit 302**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Telephone[b]**	**Telephone**
Measure vital signs (including body temperature)	X	X			
Perform clinical assessment[c]	X	X			
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X			
Obtain randomization number and study intervention allocation	X				
Obtain anterior nasal swab	X	X			
Collect blood sample for potential troponin level testing	~5 mL		~5 mL		
Administer study intervention	X	X			
Assess acute reactions for at least 30 minutes after study intervention administration	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			
Ensure the participant's parent(s)/legal guardian has a caliper device and thermometer		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			
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	

Visit Number	301	302	303	304	305
Visit Description	**Dose 1[a]**	**Dose 2**	**4-Day Follow-up Visit**	**1-Month Follow-up Visit**	**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**	**175 to 189 Days After Visit 302**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Telephone[b]**	**Telephone**
Collect AEs as appropriate[d]	X	X	X	X	
Collect SAEs as appropriate[e]	X	X	X	X	X
Unblind the participant and move to either Section 1.3.5.1 or continue on this SoA as appropriate[f]					X
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; SMS = short message service; SoA = schedule of activities.

a. This visit may be conducted across 2 consecutive dates; if so, please refer to Section 8.11.7.1.
b. 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.
c. Including, if indicated, a physical examination.
d. 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).
e. Refer to Section 8.3.1 for the time period for collecting SAEs.
f. This is applicable to the 5- to <12-year-old age group (placebo-controlled).

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

Visit Number	A1	B1	C1	D1
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**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**	**175 to 189 Days After Visit B1**
Type of Visit	**Clinic**	**Clinic**	**Telephone[b]**	**Telephone**
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
Confirm use of contraceptives (if appropriate)	X	X	X	
Collect prohibited medication use	X	X	X	X
Review and consider eligibility	X	X		
Review temporary delay criteria	X	X		
Measure vital signs (including body temperature)	X	X		
Perform clinical assessment[c]	X	X		
Perform urine pregnancy test (only for female participants biologically capable of having children)	X	X		
Obtain anterior nasal swab	X	X		
Collect blood sample for potential troponin level testing	X[d]			
Obtain vaccine vial allocation via IRT	X			
Administer BNT162b2	X	X		
Assess acute reactions for at least 30 minutes after study intervention administration	X	X		

Visit Number	A1	B1	C1	D1
Visit Description	**Dose 3**	**Dose 4**	**1-Month Follow-up Visit**	**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**	**175 to 189 Days After Visit B1**
Type of Visit	**Clinic**	**Clinic**	**Telephone[b]**	**Telephone**
Collect AEs as appropriate[e]	X	X	X	
Collect SAEs as appropriate[f]	X	X	X	X

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

a. For participants who become eligible according to recommendations detailed separately and available in the electronic study reference portal.
b. 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.
c. Including, if indicated, a physical examination.
d. 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.
e. 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).
f. 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.

With the robust immune responses elicited in adolescents with BNT162b2, the purpose of the lower-dose evaluation is to determine whether additional lower dose levels of BNT162b2 (3 µg, 10 µg) will not only to minimize reactogenicity and risk of other AEs but as well to potentially unify the dose levels across children and young adults.

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. 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.

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. With the robust immune responses elicited in adolescents to minimize reactogenicity and the risk of other AEs and to potentially unify the dose levels across children and young adults, additional lower dose levels of BNT162b2 (3 µg, 10 µg) will be evaluated to determine whether similar immune responses are elicited. For this lower-dose evaluation portion, a new cohort of Phase 1 participants will be enrolled in 3 age groups: >5 to <12, 12 to <16, 16 to <30 years of age to assess safety, tolerability, and immunogenicity. The Phase 2/3 BNT162b2 dose level 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.

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 study[25] 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.[26] Vaccine-related enhanced disease for vaccines against related coronaviruses (SARS-CoV-1 and MERS) has been reported only in animal models.[27,28] 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]

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. The most common events reported in the C4591001 study were mild to moderate pain at the injection site, fatigue, and headache.	• 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.
The safety profile of a novel vaccine is not yet fully characterized. 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).	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. 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.	• 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential for COVID-19 enhancement.	Disease enhancement has been seen following RSV, feline coronavirus, and dengue virus vaccinations. No evidence of disease enhancement has been seen in a large-scale clinical study of BNT162b2 in humans or in postauthorization surveillance.	• No evidence of disease enhancement has been reported in the C4591001 study to date.[26] Temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants, with the exception of Phase 2/3 lower-dose evaluation participants, are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 neutralizing titers. • For Phase 1/2/3 lower-dose evaluation participants, cases of COVID-19 developing during the study are monitored and will be reported as AESIs.
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: The estimated rate is 5.0 per million doses administered. Myocarditis and pericarditis: Very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.	Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected. For anaphylaxis, there is an on-site 30-minute observation period after vaccination. Instructions for handling suspected cases of myocarditis and pericarditis are found in Section 8.14.

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. To minimize the total amount of blood drawn, all participants in Phase 1 and participants contributing to the immunogenicity analysis in Phase 2/3 will have at most 3 planned blood draws, with all remaining participants having 2 planned blood draws.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

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

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures 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 lower-dose age groups referred to in the objectives and estimands below are a separate cohort of participants ≥5 to <12 years, 12 to <16 years, and 16 to <30 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.	In participants receiving at least 1 dose of study intervention, the percentage of participants in each age group reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	Participants 16 to <30, 12 to <16, ≥5 to <12, and ≥2 to <5 years of age: • 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: • 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.	In participants complying with the key protocol criteria (evaluable participants) in each age group: • GMTs at 7 days after Dose 2	• 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.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection.		• 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, lower-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: • 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	Participants 16 to <30, 12 to <16, ≥5 to <12, and ≥2 to <5 years of age: • 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: • Local reactions (tenderness at the injection site, redness, and swelling) • Systemic events (fever, decreased appetite, drowsiness, and irritability) • AEs • SAEs
Primary Immunogenicity (Selected-Dose):	**Primary Immunogenicity (Selected-Dose):**	**Primary Immunogenicity (Selected-Dose):**
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:	• SARS-CoV-2 neutralizing titers
• 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.	• 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**
• 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.	• 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	
• 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.	• 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	
Secondary Immunogenicity (Lower-Dose Evaluation):	**Secondary Immunogenicity (Lower-Dose Evaluation):**	**Secondary Immunogenicity (Lower-Dose Evaluation):**
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the lower dose level 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:	• SARS-CoV-2 neutralizing titers
• 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.	• 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 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 ≥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**
• In participants 12 to <16 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study.	• GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants 12 to <16 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 12 to <16 years of age and participants 16 to 25 years of age from Phase 2/3 of the C4591001 study	
• In participants 16 to <30 years of age compared to participants 16 to 55 years of age from Phase 2/3 of the C4591001 study.	• GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants 16 to <30 years of age to those in participants 16 to 55 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 16 to <30 years of age and 16 to 55 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 and persistence of immune response 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: At baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 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:	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of blinded follow-up
• 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.	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
• In the ≥6 months to <2 years and ≥2 to <5 years age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups.	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
• In all age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups and if the above 2 individual age groups (≥5 to <12 years, ≥6 months to <2 years and ≥2 to <5 years combined) did not accrue 21 cases.	• 100 × (1 – 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 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:	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of blinded follow-up
• 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.	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
• In ≥6 months to <2 years and ≥2 to <5 years age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups.	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
• In all age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups and if the above two individual age groups (≥5 to <12 years of age, ≥6 months to <2 years and ≥2 to <5 years combined) did not accrue 21 cases.	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection.	In evaluable participants without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 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 all age groups combined.	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 at the dose level selected in each age group and persistence of immune response 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: At baseline and at 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMCs and/or GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• Full-length S-binding IgG levels and/or 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.		• 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.		• Confirmed cases as per CDC criteria

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
To describe the serological responses in Phase 2/3 participants in participants in the selected-dose portion of the study to BNT162b2 at the dose level selected in each age group in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 neutralizing titers
To describe the safety and immunogenicity of prophylactic BNT162b2 at the dose level selected in each age group in children with stable HIV disease.		• All safety and immunogenicity endpoints described above will be analyzed descriptively
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain in a subset of participants: • At baseline and at 7 days and 6 months after Dose 2		
To describe the frequency of elevated troponin I levels at baseline and after Vaccination 2 if testing is indicated based upon data accrued outside of this study.		

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 ≥4 × 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 <30 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, Lower-Dose Evaluations, and Obtaining Serum Samples for Potential Troponin I Testing

Phase 1 Open-Label Dose-Finding Evaluation						
	≥6 Months to <2 Years	**≥2 to <5 Years**	**≥5 to <12 Years**	**12 to <16 Years**	**16 to <30 Years**	**Total**
Dose level	3 µg	3/10 µg	10/20/30 µg			
Participants	16[a]	16/32[a]	16/16/16[b]			112
Phase 2/3 Observer-Blinded, Placebo-Controlled Selected-Dose Evaluation						
Dose level	3 µg	3 µg	10 µg			
Participants	2250 (active 1500; placebo 750)	2250 (active 1500; placebo 750)	4500 (active 3000; placebo 1500)			9000
Phase 1 Open-Label Lower-Dose Evaluation						
Planned dose level(s)			3 µg	3/10 µg[c]	3/10 µg[c]	
Participants			32	32/32	32/32	160
Phase 2/3 Open-Label Lower-Dose Evaluation						
Planned dose level			TBD	TBD	TBD	
Participants			300	300	300	900
Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing						
Planned dose level			10 µg	30 µg		
Participants			750 (active 500; placebo 250)	500 (active 500; placebo 0)		1250

a. Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
b. 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.
c. Both dose levels will start concurrently.

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.

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 the Phase 2/3.

Lower-dose evaluation: Is the open-label lower-dose evaluation portion of the study that will evaluate safety, tolerability, and immunogenicity of BNT162b2 on a 2-dose (separated by approximately 21 days) schedule in up to 3 age groups (participants ≥5 to <12 years, 12 to <16 years, and 16 to <30 years of age).

The purpose of the Phase 1 lower-dose evaluation is to evaluate safety and immunogenicity of BNT162b2 from up to 2 different dose levels in each age group.

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 the Phase 2/3 lower-dose evaluation portion of the study.

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 and 6 months after Dose 2. Immunobridging to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2.

The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and at 1, 6, 12 (original BNT162b2 group only), and 24 months after Dose 2 (original BNT162b2 group only). In addition, efficacy against confirmed COVID-19 and against asymptomatic 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. 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. 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 have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time at the approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study.

Lower-dose evaluation: 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 lower-dose evaluation.

In this open-label study, all participants will have blood drawn at baseline prior to Dose 1 and at 1 and 6 months after Dose 2. Immunobridging to comparator participants in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and 1 and 6 months after Dose 2.

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.

4.1.3. Number of Participants

4.1.3.1. Phase 1: Open-Label Dose-Finding and Lower-Dose Evaluation

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 and a minimum of 32 participants per dose level (total of 160 participants) for the lower-dose evaluation; see Table 2 and Table 3.

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.

Table 3. Phase 1 Lower-Dose Evaluation Participants

Age Group	Total	Up to 2 Dose Levels of BNT162b2[a]	Active	Placebo
≥5 to <12 Years	32	32	32	N/A
12 to <16 Years	64	32/32	32	N/A
16 to <30 Years	64	32/32	32	N/A

a. A dose level may be expanded to enroll more than 32 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 9000 participants as an additional 2250 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 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 will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure this subset is representative of the whole study.

For the persistence time points of 12 and 24 months after Dose 2, approximately 70 participants from each age group in the original BNT162b2 group will have an immunogenicity blood draw in order to contribute to the analysis. All approximately 9000 participants will contribute to the VE analysis for conditional VE.

Approximately 4500 participants who had post–Dose 1 blood sample collection will contribute to the asymptomatic infection analysis. 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.

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. These samples will be used on an exploratory basis to investigate the postvaccination cell-mediated immune response at these time points.

Table 4. Phase 2/3 Selected-Dose Participants – 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	9000	6000	3000	4500	3000	1500	2250	1500	750
1 Month after Dose 2	1350	900	450	450	300	150	450	300	150
6 Months after Dose 2	4500	3000	1500	2250	1500	750	1125	750	375
12 Months after Dose 2	210	210	N/A	70	70	N/A	70	70	N/A
24 Months after Dose 2	210	210	N/A	70	70	N/A	70	70	N/A

a. Number of participants shown is for each of these 2 younger age groups.

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	2250	1500	750
≥6 Months to <2 Years	2250	1500	750
All age groups	9000	6000	3000

Lower-dose evaluation: Is the open-label 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 lower-dose evaluation, with a total of approximately 900 active participants (Table 6).

Approximately 300 active participants in each age group in this phase will contribute to the immunobridging analysis at 1 month after Dose 2 and the overall analysis of the persistence

of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure this subset is representative of the whole study.

Table 6. Phase 2/3 Lower-Dose Evaluation Participants – Blood Draws for Immunogenicity/Efficacy Assessments

	All Age Groups		⩾5 to <12, 12 to <16 Years, and 16 to <30 Years of Age[a]	
	Total	Active	Active	Placebo
Baseline blood draw	900	900	300	N/A
1 Month after Dose 2	900	900	300	N/A
6 Months after Dose 2	900	900	300	N/A

a. Number of participants shown is for each age group.

All participants will contribute to the safety, tolerability, and efficacy assessments (Table 7).

Table 7. Phase 2/3 Lower-Dose Evaluation Participants – Safety and Tolerability/Efficacy Assessments

Total	Active	Placebo
900	900	N/A

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

4.1.4. 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.

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: Participants are expected to participate for up to a maximum of approximately 26 months.

Phase 1 lower-dose evaluation: As safety has been assessed at higher dose levels in all 3 age groups, each dose and age level will occur concurrently:

- ≥5 to <12 Years: 3 µg
- 12 to <16 Years, 16 to <30 Years: 3 µg and 10 µg

The IRC will review safety data (e-diary and AEs) acquired up to 7 days after Dose 2.

Phase 2/3 lower-dose evaluation: 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: Participants are expected to participate for up to a maximum of approximately 6 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 6 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 lower-dose evaluation, 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).

Lower-dose evaluation (participants 5 to <12, 12 to <16, 16 to <30 years of age): 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 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. With the robust immune responses elicited in adolescents to minimize reactogenicity and risk of other AEs and to potentially unify the dose levels across children and young adults, additional lower dose levels of BNT162b2 (3 µg, 10 µg) will be evaluated

to determine whether similar immune responses are elicited. For this lower-dose evaluation portion, a new cohort of Phase 1 participants will be enrolled in 3 age groups: >5 to <12, 12 to <16, 16 to <30 years of age to assess safety, tolerability, and immunogenicity. The Phase 2/3 BNT162b2 dose level will be selected based on the Phase 1 assessments with an immunobridging analysis of immune responses in participants within each age group to participants in the 30-µg Phase 3 C4591001 efficacy study.

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

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

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 and between ≥5 and <30 years of age, at the time of randomization, at Visit 1 for the lower-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.

5.3.2. Strenuous or Endurance Exercise (Potential Troponin I Testing Group Only)

Participants should avoid participation in age-appropriate strenuous or endurance exercise from 4 days prior to Visit 1 through Visit 1 and from Visit 2 through Visit 3 (eg, hiking uphill or with a heavy backpack, high-intensity muscle-strengthening activity [such as resistance or weights], running, swimming laps, aerobic dancing, heavy yardwork such as continuous digging or hoeing, tennis [singles], cycling 10 miles per hour or faster, or jumping rope). If a participant has undertaken strenuous exercise during this time period, this would be considered a protocol deviation and noted in the source documents.

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 ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness (<u>for Phase 1, confirmed COVID-19 diagnosis is an exclusion criterion</u>):

    - New or increased cough;
    - New or increased shortness of breath;
    - Diarrhea;
    - Vomiting;

- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Nausea;
- Inability to eat/poor feeding in participants <5 years of age.

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 vaccine between Doses 1 and 2, or between Doses 3 and 4, of study intervention, or within 7 days after Dose 2 or 4.

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 lower-dose evaluation and obtaining-serum-samples-for-potential-troponin I-testing (12 to <16 years old) portions are open-label.

Phase 1 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 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)	Saline Placebo (Selected-Dose)
Type	Vaccine	Placebo
Dose Formulation	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10 µg, 20 µg, or 30 µg, with an option for 3 µg or another dose level	N/A
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement.	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, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/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 Doses 1 and 2 in 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 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. 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 have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study.

For the participants in Phase 1 and in the Phase 2/3 lower-dose evaluation and 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 for Doses 1 and 2 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 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 1.3.3.2 and Section 1.3.5.1 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 (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 any vaccine between Doses 1 and 2, or between Doses 3 and 4, of study intervention, or within 7 days after Dose 2 or 4.

- 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 Visit 4 (1-month follow-up after Dose 2).

- 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 for Phase 1 dose-finding participants and Visit 5 for Phase 2/3 selected-dose participants; Visit 105 for Phase 1 and Visit 204 for Phase 2/3 lower-dose evaluation participants; and Visit 305 for Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing participants; Visit D and Visit D1 for 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, respectively).

- 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.

- 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.

6.6. 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 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.
- 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).

6.7. 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 (including to receive a BNT162b2 30-µg dose outside of the study); 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.

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, 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 15 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 10-mL blood draw. 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 45 mL. Phase 1 and Phase 2/3 lower-dose evaluation participants 12 to <16 years of age will have an individual total blood sampling volume of approximately 30 mL, and those >16 years of age

will have an individual total blood sampling volume of approximately 60 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.[29] 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 pain[11];
- Lethargy.

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 8[30]; SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg);

Table 8. 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

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

Participant Age	RR	HR
8 to <12 Years	>25	>115

Abbreviations: HR = heat 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.

- Respiratory failure (defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
    - SBP (mm Hg):
        - <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or requiring vasoactive drugs to maintain BP in the normal range;
- Significant acute renal failure: Serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine;
- Significant GI/hepatic failure: 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 baseline[32];
- 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,[31] as per the CDC MIS-C case definition:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, acute kidney injury);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
    - Dermatologic (eg, rash, mucocutaneous lesions);
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR
- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

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

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

- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

8.1.1. 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, and at 7 days and 6 months after Dose 2, 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 and Dose 2). 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.

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.[29]

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 9. 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 9. 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 9.

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 9. 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

Table 9. Local Reaction Grading Scale

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

Abbreviation: IV = intravenous.

a. 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 11.

Table 11. 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 ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 12 during analysis.

If a fever of ≥39.0°C (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C (>104.0°F). If a participant experiences a confirmed fever >40.0°C (>104.0°F), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 12. Scale for Fever

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

8.2.4.5. 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°C (>104.0°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

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. In addition, any AEs occurring up to 48 hours after each subsequent blood draw and nasal swab collection must be recorded on the CRF.

SAEs will be collected from the time the participant 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.

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 lower-dose evaluation and obtaining-serum-samples-for-potential-troponin I-testing portion of the study**: Confirmed COVID-19 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.

Phase 2/3 Participants Who Originally Received Placebo:

At the 6-month follow-up visit, all participants will be unblinded and if they originally received placebo will be offered BNT162b2. 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 have the opportunity to receive

BNT162b2 (10 µg or 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study. For participants who originally received placebo and go on to receive BNT162b2 as Dose 3 and Dose 4, the time period for actively eliciting and collecting AEs and SAEs will continue from the receipt of BNT162b2 (Dose 3 and Dose 4) through and including 1 month after Dose 4. SAEs will be collected from the time of receipt of BNT162b2 (Dose 3 and Dose 4) through approximately 6 months after Dose 4 of BNT162b2.

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 <u>not</u> 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 lower-dose evaluation or obtaining-serum-samples-for-potential-troponin I-testing participants only).
- Confirmed MIS-C diagnosis (applicable to lower-dose evaluation or 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 before vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and before 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 before vaccination, measure the participant's vital signs (including body temperature).
- On the day of and before 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°C (≥102.1°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 before vaccination, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- On the day of and before vaccination, measure the participant's vital signs (including body temperature).

- On the day of and before 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 before 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 before 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 ≥39.0°C (≥102.1°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 6 – 12-Month Follow-up Visit (350 to 378 Days After Visit 2)

- Contact the participant's parent(s)/legal guardian by telephone.
- 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 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.

8.11.1.7. Visit 7 – 24-Month Follow-up Visit (714 to 742 Days After Visit 2)

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.
- 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 1 Lower-Dose Evaluation

8.11.2.1. Visit 101 – 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 or 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. 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 before vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and before 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 before vaccination, measure the participant's vital signs (including body temperature).

- On the day of and before 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 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 for immunogenicity.

    - 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.

- 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.

- 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 or 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°C (≥102.1°F).
  - Redness or swelling at the injection site >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 or 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.
- 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.

8.11.2.2. Visit 102 – Dose 2 (19 to 23 Days After Visit 101)

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 before 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 a nasal (anterior nares) swab (collected by site staff).
- On the day of and prior to vaccination, collect a blood sample for immunogenicity testing.
    - 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.
- 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 or 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 or participant's parent(s)/legal guardian remain comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant or 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 or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site >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 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 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.

8.11.2.3. Visit 103 – 7-Day Follow-up Visit (1 Week After Dose 2, 6 to 8 Days After Visit 102)

- Review the participant's reactogenicity e-diary data.
- 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).
- 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.
- On the day of and prior to vaccination, collect a blood sample for immunogenicity testing.
    - 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.
- 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.

8.11.2.4. Visit 104 – 1-Month Follow-up Visit (28 to 35 Days After Visit 102)

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.
- 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 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.

8.11.2.5. Visit 105 – 6-Month Follow-up Visit (175 to 189 Days After Visit 102)

- 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.
- 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.

8.11.3. Phase 2/3 Selected-Dose Portion

8.11.3.1. 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.
- Obtain the participant's medical history of clinically 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 before vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and before vaccination, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and before vaccination, measure the participant's vital signs (including body temperature).
- On the day of and before 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 ≥39.0°C (≥102.1°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.

8.11.3.2. 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 before 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 ≥39.0°C (≥102.1°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.

8.11.3.3. 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.

8.11.3.4. 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.

- 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 since Visit 1 (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.

- 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.

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

- 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 since Visit 4 (if any).
- Collect a blood sample (approximately 5 mL) for immunogenicity testing.
    - Not required for the additional 2250 participants included to enlarge the size of the pediatric safety database.
- 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.
- 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, complete this visit for the remainder of visit activities and schedule an appointment for the participant for the next study visit as in Section 8.11.4.
    - If the participant originally received placebo, move the participant to Section 8.11.5 for the remainder of this visit's activities and future 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.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.4. Phase 2/3 Selected-Dose Portion: Participants Who Originally Received BNT162b2 or Placebo Recipients Who Decline BNT162b2

8.11.4.1. Visit X – 12-Month Follow-up Visit (350 to 378 Days After Visit 2)

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 since Visit 5 (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.
- 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.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.4.2. Visit Y – 24-Month Follow-up Visit (714 to 742 Days After Visit 2)

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 since Visit X (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.
- 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.
- If applicable, record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.
- 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

8.11.5.1. Visit A – Dose 3 (175 to 189 Days After Dose 2 and Same Date as Visit 5)

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. It is preferable that this visit occur on the same day as Visit 5.

- Confirm that the participant meets local/national recommending criteria or is at least 175 days after Dose 2 (Visit 2).
- 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 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 before 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, 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 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 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 before 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.

8.11.5.3. 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 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 since Visit A (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.

8.11.5.4. Visit D – 6-Month Follow-up Telephone Contact (After Dose 4) (175 to 189 Days After Visit B)

- 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 since Visit C (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 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.

8.11.5.5. Visit E – 12-Month Follow-up Telephone Contact (After Dose 4) (350 to 378 Days After Visit B)

- Contact the participant's parent(s)/legal guardian by telephone.
- 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 since Visit D (if any).
- 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 F – 18-Month Follow-up Telephone Contact (After Dose 4) (532 to 560 Days After Visit B)

- This visit can be performed as a telephone visit.
- 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 since Visit E (if any).
- 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 Lower-Dose Evaluation

8.11.6.1. Visit 201 – 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 or 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 clinically 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 before vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and before vaccination, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and before vaccination, measure the participant's vital signs (including body temperature).
- On the day of and before 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 for immunogenicity testing.

    - 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.

- 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 or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring >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 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 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.

8.11.6.2. Visit 202 – Dose 2 (19 to 23 Days After Visit 201)

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

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

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring >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 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 to return for the next study visit.

- Remind the participant or 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 203 – 1-Month Follow-up Visit (After Visit 2) (28 to 35 Days After Visit 202)

- 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 since Visit 1 (if any).
- Discuss contraceptive use as described in Section 5.3.1.
- Collect a blood sample for immunogenicity testing if the participant is in the group where blood collection at this visit is required.
    - 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.
- 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.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

8.11.6.4. Visit 204 – 6-Month Follow-up Visit (175 to 189 Days After Visit 202)

- Record AEs and 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 since Visit 4 (if any).

- Collect a blood sample for immunogenicity testing.
    - 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to <16 years of age; 5 mL is to be collected from participants 5 to <12 years of age.
- 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.
- 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 or participant's parent(s)/legal guardian to remove the study application from his or her own personal device.
- Inform the participant or participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11.7. 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)

8.11.7.1. 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 clinically 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 before vaccination, ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- On the day of and before vaccination, ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- On the day of and before vaccination, measure the participant's vital signs (including body temperature).
- On the day of and before 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 ≥39.0°C (≥102.1°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.

8.11.7.2. 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 before 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 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 ≥39.0°C (≥102.1°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.

8.11.7.3. 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.

8.11.7.4. 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 since Visit 1 (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.

8.11.7.5. Visit 305 – 6-Month Follow-up Visit (175 to 189 Days After Visit 302)

- Contact the participant's parent(s)/legal guardian by telephone.
- 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 since Visit 4 (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 8.11.8 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.

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

8.11.8.1. 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. It is preferable that this visit occur on the same day as Visit 305.

- 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 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 before 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 a nasal (anterior nares) swab (collected by site staff).
- 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.

8.11.8.2. 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 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 before 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 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.

8.11.8.3. 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 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 since Visit A1 (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's parent(s)/legal guardian to contact the site staff or investigator 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.

8.11.8.4. Visit D1 – 6-Month Follow-up Visit (175 to 189 Days After Visit B1)

- Contact the participant's parent(s)/legal guardian by telephone.
- Record 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 since Visit C1 (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 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.

- Inform the 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 experiences 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.

- 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 8[30];

        - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/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 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or

        - requiring vasoactive drugs to maintain BP in the normal range;

- Significant acute renal failure (serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine);
- Significant GI/hepatic failure (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 baseline[32];
- 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:

- Visit 1, Visit 2, Visit A, Visit B, Visit 101, Visit 102, Visit 201, Visit 202, Visit 301, Visit 302, Visit A1, and Visit B1: 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 Visit 1, Visit 2, Visit A, and Visit B 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:

- 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.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. 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 × 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 and participants 16 to 25 years of age 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) and in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study, respectively, measured 1 month after Dose 2. 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 ≥4 × 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%.

In a similar manner, the hypothesis related to the secondary objectives of the lower-dose evaluation for each age group will be evaluated separately. Within each age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially.

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 ≥ LLOQ.

9.1.2.2. Statistical Hypothesis Evaluation for Efficacy

The secondary efficacy endpoints are to evaluate VE defined as 100 × (1 – IRR) in each of the 2 age groups (≥5 to <12 years, ≥6 months to <2 years and ≥2 to <5 years combined) or across all age groups where immunobridging success is declared (if required number of cases are not accrued in either of the 2 individual age groups) 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.

VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior infection, and VE_2 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:

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

for VE_1 and VE_2, 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 in each of the 5 age groups (16 to <30 years, 12 to <16 years, ≥5 to <12 years [selected-dose and lower-dose evaluation participants], ≥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 5 age groups.

Within each age group, except for the ≥5 to <12 years age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially in the order as specified. Within the ≥5 to <12 years age group, immunobridging based on GMR and seroresponse difference will be first assessed sequentially in participants from the selected-dose portion of the study and then assessed sequentially in participants from the lower-dose evaluation portion of the study.

In each of the 2 age groups (≥5 to <12 years, ≥6 months to <2 years and ≥2 to <5 years combined) 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, VE_1 and VE_2, will be tested sequentially in the order as stated for each age group. Thus, this sequential testing strategy controls type I error at the desired level of 2.5% within each age group. Efficacy objectives for each of the 2 age groups will be assessed separately. No type I error adjustments will be applied in the efficacy assessments for the 2 age groups for the same reason described above for immunogenicity assessments. However, if the required number (21) of confirmed COVID-19 cases is not accrued in either of the 2 age groups where immunobridging success is declared, but 21 cases are accrued across all the age groups where immunobridging success is declared, then hypothesis testing will be conducted across the age groups with immunobridging success.

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 1 lower-dose evaluation portion of the study includes a minimum of 32 participants receiving active vaccine per group for each dose level; 5 groups may be studied, corresponding to a total of 160 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 the ≥5 to <12 years age group, and 2250 (randomization ratio of 2:1 so that 1500 receive active vaccine and 750 receive placebo) for the ≥2 to <5 years age group and the ≥6 months to <2 years age group each, with a total of approximately 9000 participants. The total sample size in Phase 2/3 is not based on statistical hypothesis testing.

For the lower-dose evaluation portion of the study, Phase 2/3 will include approximately 300 participants for each age group that will receive active vaccine at the selected dose level, with a total of approximately 900 participants.

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. 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 13). 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 and 300 participants in the Phase 2/3 lower-dose evaluation portion of the study to achieve 225 evaluable participants in the active vaccine group.

Table 13. 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.

The persistence of immune response will be based on Phase 2/3 participants with baseline and 1-, 6-, 12-, or 24-month post–Dose 2 immunogenicity data. For the selected-dose portion of the study, in each age group, blood samples will be tested for approximately 450 participants at 1 month and 6 months (300 in the active vaccine group, and 150 in the placebo group), and for approximately 70 participants in the original BNT162b2 group at 12 or 24 months after Dose 2. Assuming a nonevaluable rate of 25%, there will be ~225 and ~50 evaluable participants at 1 and 6 months, and later time points, respectively. For the Phase 2/3 lower-dose evaluation portion of the study, blood samples will be tested for approximately 300 participants at 1 month and 6 months after Dose 2 for each age group, resulting in ~225 evaluable participants.

Table 14 displays the ratio of the upper 2-sided 95% confidence limit of GMT relative to the GMT as a measure of precision for the immunogenicity endpoint SARS-CoV-2 neutralizing titer. With 50 evaluable participants in the vaccine group, the upper 95% confidence limit of the GMT would be 20% higher than the corresponding GMT.

Table 14. Precision of SARS-CoV-2 Neutralizing Titer GMT

Standard Deviation (Log Value)[a]	Upper 2-Sided 95% Confidence Limit of GMT Relative to GMT × 100	
	50 Evaluable Participants	225 Evaluable Participants
0.65	1.20	1.09

Abbreviation: GMT = geometric mean titer.

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

For VE evaluation, 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%. If immunobridging success can be 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 the VE will be assessed by combining these 2 age groups, resulting in a total of approximately 11 confirmed COVID-19 illness cases within 6 months after vaccination. Across all age groups, a total of approximately 21 confirmed COVID-19 illness cases will be observed 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, or all age groups combined if the required number of cases is not

accrued in either of the 2 individual age groups) in which immunobridging is shown to be successful (Table 15).

Table 15. 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%)**
85.1%	25	9:16 (71.9%)
93.8%	33	13:20 (67.5%)

Abbreviation: VE = vaccine efficacy.

a. Case split numbers represent the number of cases in the active vaccine group vs the number of cases in the placebo group.

b. Success criterion: lower bound of 95% CI for VE >30%.

For safety outcomes, Table 16 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 16. 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=900	N=3000	N=6000
0.01%	0.00	0.00	0.01	0.09	0.26	0.45
0.02%	0.00	0.01	0.03	0.16	0.45	0.70
0.04%	0.01	0.01	0.06	0.30	0.70	0.91
0.06%	0.01	0.02	0.08	0.42	0.83	0.97
0.08%	0.01	0.03	0.11	0.51	0.91	0.99
0.10%	0.02	0.03	0.13	0.59	0.95	>0.99
0.15%	0.02	0.05	0.19	0.74	0.99	>0.99
0.20%	0.03	0.06	0.25	0.83	>0.99	>0.99
0.25%	0.04	0.08	0.30	0.89	>0.99	>0.99
0.30%	0.05	0.09	0.35	0.93	>0.99	>0.99
0.35%	0.05	0.11	0.40	0.96	>0.99	>0.99
0.50%	0.08	0.15	0.51	0.99	>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

Table 16. 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=900	N=3000	N=6000
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. In the Phase 1 lower-dose evaluation portion of the study, 32 participants per dose level in each age group and a total of 160 participants are to be vaccinated. Approximately 3000 participants 5 to <12 years of age and 1500 participants 6 months to <2 years and ≥2 to <5 years of age will receive the active vaccine at the selected dose level in the Phase 2/3 selected-dose portion of the study. A total of 6000 and 900 participants, in the Phase 2/3 selected-dose and lower-dose evaluation portions of the study, respectively, 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	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.
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	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccinations as randomized, receiving Dose 2 within the predefined window, have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
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.

Population	Description
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, or all age groups combined if the required number of cases is not accrued in either of the 2 individual age groups) in which immunobridging success is declared.

CIs 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	• 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 will be provided for each vaccine group. A 3-tier approach will be used to summarize AEs 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 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. • 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 will be provided for each vaccine group. • AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 or no later than at approximately the 6-month post–Dose 2 visit.

Endpoint	Statistical Analysis Methods
Immunogenicity (Phase 2/3 selected-dose portion of the study)	**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** • 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) to the 16- to 25-year age group 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) 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. **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** • The percentages of participants with seroresponse at 1 month after Dose 2 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 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) 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 ≥ LLOQ.

9.4.3. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Immunogenicity (Phase 1)	**GMTs of SARS-CoV-2 neutralizing titers** • For SARS-CoV-2 neutralizing titers, GMTs and 2-sided 95% CIs will be provided for each vaccine group at 7 days after Dose 2. • Statistical methods are described in Section 9.4.1.2.1.
Immunogenicity (Phase 2/3 lower-dose evaluation portion of the study)	**GMR of SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years and ≥12 to <16 years of age from the lower-dose evaluation portion of this study compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study** **GMR of SARS-CoV-2 neutralizing titers in participants 16 to 30 years of age from the lower-dose evaluation portion of this study compared to participants 16 to 55 years of age from Phase 2/3 of the C4591001 study** • The GMRs at 1 month after Dose 2 described above 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) of past SARS-CoV-2 infection will be included in the analysis. • Immunobridging success will be declared for an age group if the lower bound of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8. **The difference in percentages of participants with seroresponse in participants ≥5 to <12 years and ≥12 to <16 years of age from the lower-dose evaluation portion of this study and those 16 to 25 years of age from Phase 2/3 of the C4591001 study** **The difference in percentages of participants with seroresponse in participants 16 to 30 years of age from the lower-dose evaluation portion of this study and those 16 to 55 years of age from Phase 2/3 of the C4591001 study** • The percentages of participants with seroresponse at 1 month after Dose 2 in each age group, and the difference in percentages between age groups described above 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) of past SARS-CoV-2 infection will be included in the analysis.

Endpoint	Statistical Analysis Methods
	• Immunobridging success 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 ≥ LLOQ.
Immunogenicity (Phase 2/3 selected-dose portion of the study)	**GMTs and GMFRs of SARS-CoV-2 neutralizing titers** • 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 is determined as a COVID-19 case or has a positive N-binding antibody result.
VE (Phase 2/3 selected-dose portion of the study)	**Ratios of confirmed COVID-19 illness from 7 days after Dose 2 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 years age group and for the ⩾6 months to <2 years and ⩾2 to <5 years age groups combined, or across all age groups (if required number of cases are not accrued in either of the 2 individual age groups)** • VE will be estimated by 100 × (1 - 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. 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.

Endpoint	Statistical Analysis Methods
	Ratios of confirmed COVID-19 illness from 7 days after Dose 2 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 years age group and for the ⩾6 months to <2 years and ⩾2 to <5 years age groups combined, or across all age groups (if required number of cases are not accrued in either of the 2 individual age groups) • The same analysis method used for the first VE endpoint will be applied. **Ratio of incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion in participants for the active vaccine group to the placebo group in evaluable participants without evidence of past SARS-CoV-2 infection** • VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection rate in the active vaccine group to the corresponding infection rate in the placebo group. The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method. • The analysis will be based on the evaluable efficacy (seroconversion) population without serological or virological evidence of past SARS-CoV-2 infection. Missing efficacy data will not be imputed.

9.4.4. Exploratory Endpoint(s)

Endpoint	Statistical Analysis Methods
VE (Phase 2/3 selected-dose portion of the study)	• 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 (detailed separately, and available in the electronic study reference portal). A descriptive summary of VE for confirmed COVID-19 illness from 7 days after Dose 2 through the blinded follow-up period will be provided for each age group and across all age groups by including additional follow-up data during the blinded follow-up or at the end of blinded follow-up period.

Endpoint	Statistical Analysis Methods
Safety	• Descriptive summary of all safety endpoints will be provided for children with stable HIV disease.
Immunogenicity (Phase 2/3)	• GMCs of full-length S-binding IgG levels and/or 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. • In each subset of participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19, GMTs/GMCs and GMFRs of SARS-CoV-2 neutralizing titers will be summarized using the same statistical analysis method described for the secondary immunogenicity endpoints. • Empirical RCDCs 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	• Counts and percentages of confirmed severe COVID-19 and confirmed MIS-C cases will be provided, along with the associated Clopper-Pearson 95% CIs.
Cell-mediated immune response	• 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	• Counts and percentages of participants with elevated troponin I level at baseline and after Vaccination 2 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 or approximately 300 participants in the Phase 2/3 lower-dose evaluation 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).

- 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, lower-dose evaluation, or obtaining-serum-samples-for-potential-troponin I-testing portions of the study.

- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for participants in each age group in the Phase 2/3 selected-dose or lower-dose evaluation portions 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 persistence-of-immunogenicity analysis after complete data are available in each age group or at the end of the study.

- Efficacy analysis in the ≥5 to <12 years age group or in the ≥6 months to <2 years and ≥2 to <5 years age groups combined for which immunobridging success is declared when at least 21 cases are accrued in these age groups, or efficacy analysis across all age groups for which immunobridging success is declared when at least 21 cases are accrued across all 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 may not be started
    - Whether any dose level may be terminated early
    - Whether any dose level may be expanded to enroll more than 16 participants per dose level
    - 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.

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
• 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

• 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:
  • 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.

Events Meeting the AE Definition
• 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.

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.

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

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.

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.

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 Report Form
• Facsimile transmission of the Vaccine SAE Report 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 Report 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 Report Form pages within the designated reporting time frames.

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected 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
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	creatine 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
EU	European Union

Abbreviation	Term
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
LLOQ	lower limit of quantitation

Abbreviation	Term
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
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
TBili	total bilirubin
ULN	upper limit of normal
UK	United Kingdom
US	United States
VE	vaccine efficacy

Abbreviation	Term
VAED	vaccine-associated enhanced disease
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/mm^3 (or percentage of ≥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.

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Protocol C4591007

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 <12 YEARS OF AGE

Statistical Analysis Plan
(SAP)

Version: 1

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
1/ 08 Apr 2021	Protocol Amendment 1, 05 Mar 2021	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591007. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 2 and Table 3.

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

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × 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 populations (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by the all-available efficacy population. Missing laboratory results will not be imputed.

The 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.

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for 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	In participants receiving at least 1 dose of study intervention, the percentage of participants in each age group reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	Participants ≥5 to <12 years and ≥2 to <5 years of age: • 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: • 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	In participants complying with the key protocol criteria (evaluable participants) in each age group: At baseline, before Dose 2, and 7 days after Dose 2, • GMTs at each time point • GMFR from before Dose 1 (baseline) to each subsequent time point after vaccination	• 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		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• Confirmed cases as per CDC criteria

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To define the safety profile of prophylactic BNT162b2 at the selected dose level in the participants included in the Phase 2/3 immunobridging analysis 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: • 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 1 month after Dose 2	Participants ≥5 to <12 years and ≥2 to <5 years of age: • 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: • Local reactions (tenderness at the injection site, redness, and swelling) • Systemic events (fever, decreased appetite, drowsiness, and irritability) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 at the selected dose level in <u>all participants</u> randomized 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: • 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	Participants ≥5 to <12 years and ≥2 to <5 years of age: • 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: • Local reactions (tenderness at the injection site, redness, and swelling) • Systemic events (fever, decreased appetite, drowsiness, and irritability) • AEs • SAEs

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To demonstrate immunobridging of the immune response elicited by prophylactic BNT162b2 at the dose level selected per age group in Phase 2/3 participants without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection: • 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 • 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 • 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	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: • 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 to 25 years of age 1 month after Dose 2 • 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 • 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	• SARS-CoV-2 neutralizing titers
Secondary Immunogenicity/Efficacy:	**Secondary Immunogenicity/Efficacy:**	**Secondary Immunogenicity/Efficacy:**
To describe the immune responses elicited by prophylactic BNT162b2 at the dose level selected per age group and persistence of immune response 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: At baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
In all age groups where immunobridging is successful, if at least 22 cases are accrued across those age groups: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants 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: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up
In all age groups where immunobridging is successful, if at least 22 cases are accrued across those age groups: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants 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: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants without evidence of past SARS-CoV-2 infection	In evaluable participants without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion
Exploratory:	**Exploratory:**	**Exploratory:**
To evaluate the immune response over time to prophylactic BNT162b2 at the dose level selected per age group and persistence of immune response 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: At baseline and at 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in Phase 2/3 participants with and without confirmed COVID-19 during the study		• N-binding antibody
To describe COVID-19 and severe COVID-19 cases in all participants with and without serological or virological evidence of past SARS-CoV-2 infection		• Confirmed COVID-19 cases • Confirmed COVID-19 cases resulting in hospitalization • Confirmed severe COVID-19 cases

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• Confirmed cases as per CDC criteria
To describe the serological responses in Phase 2/3 participants to BNT162b2 at the dose level selected per age group in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 neutralizing titers
To describe the safety and immunogenicity of prophylactic BNT162b2 at the dose level selected per age group in children with stable HIV disease		• All safety and immunogenicity endpoints described above will be analyzed descriptively
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain in a subset of participants: • 7 days and 1 and 6 months after Dose 2		

2.2. Study Design

This is a Phase 1/2/3 study in healthy children <12 years of age.

Dependent upon safety and/or immunogenicity data generated during the course of this study, the benefit-risk, safety, tolerability, and immunogenicity of BNT162b2 in participants <6 months of age may subsequently be evaluated.

Phase 1 is the open-label dose-finding portion of the study to evaluate the safety, tolerability, and immunogenicity of BNT162b2 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.

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 final BNT162b2 dose level for Phase 2/3.

Phase 2/3 will evaluate the safety, tolerability, and immunogenicity in each age group at the selected dose level from Phase 1. Efficacy will be evaluated across all age groups in which immunobridging is successful, depending on accrual of a sufficient number of cases across those age groups.

All participants will have blood drawn at baseline prior to Dose 1 and 6 months after Dose 2. Immunobridging to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and at 1, 6, 12 (original BNT162b2 group only), and 24 (original BNT162b2 group only) months after Dose 2. In addition, efficacy against confirmed COVID-19 and against asymptomatic infection will also be assessed.

At designated 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. 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.

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

Phase 2/3 will evaluate the safety, tolerability, and immunogenicity of the selected dose level in each age group from Phase 1, with a total of approximately 4500 participants. 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 will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure that this subset is representative of the whole study.

For the persistence time points of 12 and 24 months after Dose 2, approximately 70 participants from each age group in the original BNT162b2 vaccine group will have an immunogenicity blood draw in order to contribute to the analysis. All approximately 4500 participants will contribute to the VE analysis for conditional VE and asymptomatic infection. Efficacy will be evaluated across all age groups in which immunobridging is successful, depending on accrual of a sufficient number of cases across those age groups.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Endpoints

For participants in Phase 1, participants in the Phase 2/3 immunobridging subset, and all participants in Phase 2/3, the primary safety endpoints are as follows:

- Local reactions (redness, swelling, and pain at the injection site) for up to 7 days following each dose in each vaccine group for participants ≥5 to <12 years and ≥2 to <5 years of age
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following each dose in each vaccine group for participants ≥5 to <12 years and ≥2 to <5 years of age
- Local reactions (redness, swelling, and tenderness at the injection site) for up to 7 days following each dose in each vaccine group for participants ≥6 months to <2 years of age
- Systemic events (fever, decreased appetite, drowsiness, and irritability) for up to 7 days following each dose in each vaccine group for participants ≥6 months to <2 years of age
- AEs from Dose 1 to 1 month after Dose 2
- SAEs from Dose 1 to 6 months after Dose 2 for Phase 1 participants and all Phase 2/3 participants
- SAEs from Dose 1 to 1 month after Dose 2 for Phase 2/3 participants in the immunobridging subset

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain/tenderness at the injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 4 defines the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of each dose.

Table 4. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable	Yes (1)	No (0)
Presence of each local reaction on any day	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).
Presence of any local reaction on any day	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).

Note: Missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 14) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed for participants ≥2 to <12 years of age as absent, mild, moderate, or severe according to the grading scale in Table 5. Tenderness at the injection site will be assessed for participants ≥6 months to <2 years of age as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5. Local Reaction Grading Scale

	Participant Age	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life Threatening (Grade 4)[b]
Pain at the injection site	≥2 to <12 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	≥6 Months to <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	≥6 Months to <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

Table 5. Local Reaction Grading Scale

	Participant Age	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life Threatening (Grade 4)[b]
Swelling	≥6 Months to <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

a. Parent(s)/legal guardians of the participants experiencing local reactions >14 caliper units (>7 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 the protocol, Section 10.3.3.

For each local reaction reported for each dose, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each dose) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 5), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. However, if a reaction is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing reaction would be the date/day that the next vaccine is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day after vaccination that a reaction of any severity is reported.

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

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

3.1.1.2.1. Participants ≥2 to <12 Years of Age

The systemic events assessed and recorded in the e-diary are vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale for Participants ≥2 to <12 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
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 the protocol, Section 10.3.3.

3.1.1.2.2. Participants ≥6 Months to <2 Years of Age

The systemic events assessed and recorded in the e-diary are decreased appetite, drowsiness, and irritability; participants' parent(s)/legal guardians are to record the symptoms from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 7.

Table 7. Systemic Event Grading Scale for Participants ≥6 Months to <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)

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 the protocol, Section 10.3.3.

3.1.1.2.3. Fever

Temperatures will be taken orally for participants ≥2 to <12 years of age, and axillary for participants <2 years of age, in the evening, daily, for 7 days following each dose (Days 1 through 7, where Day 1 is the day of each dose) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 8.

Table 8. Scale for Fever

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

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

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

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

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

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after Dose 2. AEs will be categorized according to MedDRA terms.

The primary safety endpoint "AEs from Dose 1 through 1 month after Dose 2" and other AE endpoints will be summarized by SOC and PT at the participant level for each age group.

This primary safety endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose). AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time of informed consent through approximately 6 months after Dose 2. SAEs will be categorized according to MedDRA terms.

The primary safety endpoints "SAEs from Dose 1 through 6 months after Dose 2" for Phase 1 participants and all Phase 2/3 participants and "SAEs from Dose 1 through 1 month after

Dose 2" for Phase 2/3 participants in the immunobridging subset will be summarized by SOC and PT at the participant level for each age group.

3.1.2. Immunogenicity Endpoints

Phase 2/3

In participants with no serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥5 to <12 years and participants 16 to 25 years of age in Study C4591001
- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥2 to <5 years and participants 16 to 25 years of age in Study C4591001
- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥6 months to <2 years of age and participants 16 to 25 years of age in Study C4591001

Values below the LLOQ will be set to 0.5 × LLOQ for the analysis. The LLOQ value for neutralizing titers will be included in the analysis specification once it is available.

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

Phase 1

- SARS-CoV-2 neutralizing titers at baseline (before Dose 1), before Dose 2, and 7 days after Dose 2
- Fold rises in SARS-CoV-2 neutralizing titers from baseline to each subsequent time point

Phase 2/3

In participants with no serological or virological evidence of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2
- Fold rises in SARS-CoV-2 neutralizing titers from baseline to each subsequent time point after Dose 2

3.2.2. Efficacy Endpoints

Phase 2/3

- Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in participants without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection
- Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in participants with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection
- Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion in participants without serological or virological evidence of past SARS-CoV-2 infection

3.3. Exploratory Endpoints

Phase 1

- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Confirmed MIS-C cases as per CDC criteria

Phase 2/3

In participants with or without serological or virological evidence of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2
- Fold rises in SARS-CoV-2 neutralizing titers from before Dose 1 to each subsequent time point after Dose 2

Other exploratory endpoints:

- N-binding antibody
- Confirmed COVID-19 cases
- Confirmed COVID-19 cases resulting in hospitalization
- Confirmed severe COVID-19 cases

- Confirmed MIS-C cases as per CDC criteria
- SARS-CoV-2 neutralizing titers by COVID-19 and SARS-CoV-2 infection status:
    - Confirmed COVID-19
    - Confirmed severe COVID-19
    - SARS-CoV-2 infection without confirmed COVID-19

3.4. Other Endpoints

All safety and immunogenicity endpoints described above will be summarized separately for participants with confirmed stable HIV infection for Phase 2/3.

3.5. Baseline and Other Variables

Measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments.

3.5.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at Dose 1 (in years for participants ≥2 to <12 years of age, in months for participants ≥6 months to <2 years of age), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white, multiracial, and not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported). In cases where more than 1 category is selected for race, the category "multiracial" will be created and used for analysis. For Phase 2/3, BMI will also be included in the demographic variables.

Age at Dose 1 will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 10th birthday, the participant is considered to be 9 years old. For participants ≥6 months to <2 years of age, age at Dose 1 in months will be derived as (date of Dose 1 – date of birth + 1) × 12 / 365.25. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of Dose 1 for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA. Comorbidities that increase the risk for severe COVID-19 illness will be categorized based on medical history terms.

A brief targeted physical examination will include, at a minimum, measurement of height and weight, assessments of general appearance, lungs, cardiovascular system, and lymph node survey. Any findings will be recorded in the source documents and, if clinically significant, the findings will be recorded on the CRF.

3.5.2. E-Diary Transmission

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

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Details of any nonstudy vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 5 for Phase 1 participants and Visit 5 for Phase 2/3 participants).
- Details of any blood/plasma products, immunoglobulins (eg, IVIG), or immunomodulators (eg, anakinra, tocilizumab) during study participation.
- Antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, exoparin, warfarin).
- Any prescribed medication to treat potential COVID-19 or MIS-C illness cases.

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

3.6. Safety Endpoints

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety, immunogenicity, and efficacy results in the table below. For the specified criteria in each population definition that are not associated with unblinded information (randomized vaccine or vaccine actually received), data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and the classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood sample collected within an appropriate window after Dose 2 (within 6-8 days after Dose 2 for Phase 1 and within 28-42 days after Dose 2 for Phase 2/3), and have no other important protocol deviations as determined by the clinician.

Population	Description
Dose 1 evaluable immunogenicity	Phase 1 only: All eligible randomized participants who receive Dose 1 of the vaccine to which they are randomized, have at least 1 valid and determinate immunogenicity result from the blood sample collected after Dose 1 (same as visit window, ie, within 19-23 days after Dose 1) and before Dose 2, and have no other important protocol deviations before Dose 2 as determined by the clinician.
All-available immunogenicity	All participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to Dose 2.
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.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

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

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 over 10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the study interventions they were randomized for each age group.

The evaluable efficacy population will be the primary analysis population by each age group for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the study interventions to which they were randomized for each age group.

The safety analyses are based on the safety population. Participants will be summarized according to the study interventions they actually received for each age group.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

For the Phase 1 part of the study, in which only active vaccine is being administered, blinding is not applicable to the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation for Doses 1 and 2 in Phase 2/3. All laboratory personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study in Phase 2/3. Further details can be found in the protocol, Section 6.3. The timing for statistical analysis is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypothesis

The primary immunogenicity objective in Phase 2/3 is to evaluate immunobridging of the immune response to prophylactic BNT162b2 at the dose level selected 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 compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. The evaluable immunogenicity population will be used for the following hypothesis testing:

$$H_0: \ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$$

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) and in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study, respectively, measured 1 month after Dose 2.

The hypothesis for each age group will be evaluated separately. Immunobridging success 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-year age group from C4591001) is >0.67.

5.1.2. Vaccine Efficacy Hypothesis

The secondary efficacy endpoints are to evaluate VE defined as 100 × (1 – IRR) in all age groups where immunobridging success is declared. 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. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior infection, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination. The assessment of VE will be based on testing the following hypothesis:

$$H_0: VE \leq 20\% \text{ vs } H_1: VE > 20\%$$

for VE_1 and VE_2, respectively.

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

5.1.3. Multiplicity Considerations

For the primary immunogenicity objectives of immunobridging of BNT162b2 in each of 3 younger age groups (≥5 to <12 years, ≥2 to <5 years, and ≥6 months to <2 years of age) to the group 16 to 25 years of age from Phase 2/3 of the C4591001 study, the hypothesis testing for each 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, there is no increase in the type I error rate, and no type I error adjustments will be applied in the immunogenicity assessments for the 3 age groups.

In all age groups where immunobridging success is declared, if the required number of confirmed COVID-19 cases, ie, 22 cases, accrued across those age groups, then the secondary VE objectives, VE_1 and VE_2, will be tested sequentially in the order as stated. Thus, this sequential testing strategy controls type I error under the desired level of 2.5%.

5.2. General Methods

All safety and immunogenicity will be analyzed separately for each age group. VE will be evaluated by combining age groups for which immunobridging success is declared. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

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

5.2.1. Analyses for Binary Data

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

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

For Phase 2/3 only, the 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. No Tier 1 events have been identified to date for BNT162b2.

- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 1% of participants with the AE term in at least 1 vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

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

5.2.2. Analyses for Continuous Data

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

5.2.2.1. Geometric Means

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

5.2.2.2. Geometric Mean Fold Rises

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

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

5.2.2.3. 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.

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant, following the Pfizer standard of handling incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

The LLOQ for each assay will be provided by Vaccine Research and Development as part of the electronic data transfer or within the Clinical Testing Completion Memo prior to statistical analysis. Assay results above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands:
  - The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose in participants ≥5 to <12 years and ≥2 to <5 years of age for Phase 1 participants, Phase 2/3 participants in the immunobridging subset, and all Phase 2/3 participants (Section 2.1).
  - The percentage of participants reporting local reactions (redness, swelling, and tenderness at the injection site) within 7 days after each dose in participants ≥6 months to <2 years of age for Phase 1 participants, Phase 2/3 participants in the immunobridging subset, and all Phase 2/3 participants (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.

- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.

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

6.1.1.1.2. Supplemental Analyses

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

- Duration (days) of each local reaction after each dose.

- Onset day of each local reaction after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group per age group.

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

Figures:

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

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimands:

    - The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, new or worsened joint pain) within 7 days after each dose in participants ≥5 to <12 years and ≥2 to <5 years of age for Phase 1 participants, Phase 2/3 participants in the immunobridging subset, and all Phase 2/3 participants (Section 2.1).

  - The percentage of participants reporting systemic events (fever, decreased appetite, drowsiness, and irritability) within 7 days after each dose in participants ≥6 months to <2 years of age for Phase 1 participants, Phase 2/3 participants in the immunobridging subset, and all Phase 2/3 participants (Section 2.1).

- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group per age group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analyses

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

- Duration of each systemic event after each dose.
- Onset day of each systemic event after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group per age group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

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

Figures:

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

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 2 for Phase 1 participants, Phase 2/3 participants in the immunobridging subset, and all Phase 2/3 participants (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 1 month after Dose 2.
- Analysis methodology: Descriptive statistics for Phase 1, descriptive statistics and 3-tiered approach for Phase 2/3 (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs from Dose 1 through 1 month after Dose 2 will be provided for each vaccine group per age group. For both Tier 1 (if any) and Tier 2 events, the between-group difference in proportions and the associated 95% CI based on the Miettinen and Nurminen[2] method will be provided. For Tier 1 events (if any), the asymptotic p-values for the difference in proportions will be provided. For Tier 3 events, counts and percentages will be provided for each vaccine group per age group.

6.1.1.3.2. Supplemental Analyses

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group per age group.

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

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 1 through 6 months after Dose 2 for Phase 1 participants and all Phase 2/3 participants, and from Dose 1 to 1 month after Dose 2 for Phase 2/3 participants in the immunogenicity bridging subset (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 6 months after Dose 2 for Phase 1 and Phase 2/3, Dose 1 through 1 month after Dose 2 for Phase 2/3 participants in the immunobridging subset.

- Analysis methodology: Descriptive statistics (Section 5.2.1).

- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).

- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 through 6 months/1 month after Dose 2 will be provided for each vaccine group per age group.

6.1.2. Immunogenicity Endpoint (Phase 2/3)

6.1.2.1. 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

6.1.2.1.1. Main Analyses

- Estimands:

  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥2 to <5 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥6 months to <2 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after Dose 2.

- Analysis methodology: The GMRs and associated 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be the younger age group minus the group 16 to 25 years of age. Immunobridging success will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 (Section 5.2.2.3).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence of past

SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.

- Reporting results: The GMRs and associated 2-sided 95% CIs will be provided.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints (Phase 1)

6.2.1.1. SARS-CoV-2 Neutralizing Titers

6.2.1.1.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFRs from before Dose 1 to each subsequent time point after vaccination (Section 2.1).
- Analysis set: Dose 1 evaluable immunogenicity population, evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1), before Dose 2, and 7 days after Dose 2.
- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs and the associated 2-sided CIs will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point.
- Reporting results: GMTs and 2-sided 95% CIs will be provided for each vaccine group per age group before vaccination and at each subsequent time point after vaccination. GMFRs and 2-sided 95% CIs will be provided for each vaccine group per age group from before vaccination to each subsequent time point after vaccination.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers at each time point by vaccine group per age group.

6.2.2. Immunogenicity Endpoints (Phase 2/3)

6.2.2.1. SARS-CoV-2 Neutralizing Titers for Participants Without Evidence of Past SARS-CoV-2 Infection

6.2.2.1.1. Main Analyses

- Estimands:
  - GMTs in participants with no serological or virological evidence of past SARS-CoV-2 infection (Section 2.1).
  - GMFRs from before Dose 1 to each subsequent time point after Dose 2 in participants with no serological or virological evidence of past SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2.
- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs and the associated 2-sided CIs will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. Only participants with no serological or virological evidence of past SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.
- Reporting results: GMTs and 2-sided 95% CIs will be provided for each vaccine group per age group before vaccination and at each subsequent time point after Dose 2. GMFRs and 2-sided 95% CIs will be provided for each vaccine group per age group from before vaccination to each subsequent time point after Dose 2.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers at each time point for each vaccine group per age group.

6.2.3. Vaccine Efficacy Endpoints (Phase 2/3)

6.2.3.1. COVID-19 Incidence per 1000 Person-Years of Blinded Follow-up

6.2.3.1.1. Main Analyses

- Estimands:
  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants without evidence of past SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants with or without evidence of past SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).
- Analysis methodology: Assessment of VE will be performed for confirmed COVID-19 illness (using the first definition in Appendix 2) from 7 days after Dose 2, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group (see Appendix 2 for details on the derivation of IRR and VE). The hypothesis test for the VE objective will be performed if at least 22 cases are accrued at the time of analyses.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided for pooled age groups where immunobridging success is declared.

6.2.3.1.2. Supplemental Analyses

The same assessment of VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time for pooled age groups will be performed for confirmed COVID-19 illness based on CDC-defined symptoms (using the second definition in Appendix 2).

6.2.3.2. Incidence of Asymptomatic Infection of SARS-CoV-2 Based on N-Binding Antibody Seroconversion in Participants Without Evidence of Past SARS-CoV-2 Infection

6.2.3.2.1. Main Analyses

- Estimand:
  - 100 × (1 - IRR) [ratio of asymptomatic infection based on the N-binding antibody seroconversion per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (seroconversion) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Assessment of VE will be performed for the incidence of asymptomatic infection of SARS-CoV-2, and will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of incidence of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group (see Appendix 3 for details on the definition of asymptomatic infection and the derivation of IRR and VE).
- Intercurrent events and missing data: Missing N-binding data will not be imputed.
- Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided for pooled age groups where immunobridging success is declared.

6.3. Exploratory Endpoints

6.3.1. Immunogenicity Endpoints (Phase 2/3)

6.3.1.1. Main Analyses

- GMTs and GMFRs of SARS-CoV-2 neutralizing titers will be summarized for each vaccine group per age group in participants with or without serological or virological evidence of past SARS-CoV-2 infection using the same statistical analysis method described for the secondary immunogenicity endpoints.
- GMTs and GMFRs of SARS-CoV-2 neutralizing titers will be summarized for each vaccine group per age group in each subset of participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19 using the same statistical analysis methods described for the secondary immunogenicity endpoints.

6.3.2. N-Binding Antibody and COVID-19 Cases

6.3.2.1. Main Analyses

- Estimands:

  Phase 1

  - Confirmed COVID-19 cases (Section 2.1).
  - Confirmed severe COVID-19 cases (Section 2.1).
  - Confirmed MIS-C cases as per CDC criteria (Section 2.1).

  Phase 2/3

  - N-binding antibody (Section 2.1).
  - Confirmed COVID-19 cases (Section 2.1).
  - Confirmed COVID-19 cases resulting in hospitalization (Section 2.1).
  - Confirmed severe COVID-19 cases (Section 2.1).
  - Confirmed MIS-C cases as per CDC criteria (Section 2.1).

- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of confirmed COVID-19 cases (using the first definition in Appendix 2), confirmed COVID-19 cases resulting in hospitalization (using the first definition in Appendix 2), confirmed severe COVID-19 cases (using the first definition in Appendix 2), confirmed MIS-C cases as per CDC criteria, and N-binding antibody will be provided.

6.3.2.2. Supplemental Analyses

The same analyses will be performed for confirmed COVID-19 (using the second definition in Appendix 2), confirmed COVID-19 cases resulting in hospitalization (using the second definition in Appendix 2), and confirmed severe COVID-19 (using the second definition in Appendix 2).

6.4. Other Endpoints

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively for Phase 2/3.

The AEs, including SAEs, reported in the open-label follow-up period will be summarized separately from those reported during the blinded follow-up period.

6.5. Subset Analyses

Subgroup analyses based on sex, race, and ethnicity will be performed on all primary safety and immunogenicity endpoints (as supplemental analyses).

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

6.6.1.1. Demographic Characteristics

Demographic characteristics, including age at Dose 1, sex, race, ethnicity, and classification of BMI, will be summarized for the safety population for each vaccine group and overall per age group.

6.6.1.2. Medical History

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

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (Doses 1 and 2), who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment) per age group. The reasons for withdrawal will be those as specified in the database.

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

6.6.2.2. Blood Samples for Assay

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

6.6.2.3. Transmission of E-Diaries

The participants who were vaccinated and have completed e-diaries after each dose will be summarized according to the vaccine actually received. The summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for each dose according to the vaccine actually received per age group.

The safety population will be used.

6.6.3. Study Vaccination Exposure

6.6.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for all randomized participants per age group. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall per age group.

In addition, the relation of randomized vaccine to vaccine actually received will be presented as a cross tabulation of the vaccine actually received versus the randomized vaccine per age group.

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

6.6.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before Dose 1 will be listed. The number and percentage of participants receiving each concomitant vaccine after Dose 1 will be tabulated by vaccine group per age group. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.7. Safety Summaries and Analyses

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs, are described under the Primary Endpoints (see Section 6.1).

7. 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.

7.1. Analysis Timings

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.
- Safety data through 1 month after Dose 2 from the approximately 450 participants in Phase 2/3 included in the immunobridging analysis in each age group.
- Immunogenicity data through 1 month after Dose 2 from the approximately 450 participants in Phase 2/3 included in the immunobridging analysis in each age group (immunobridging analysis of SARS-CoV-2 neutralizing titers in each age group compared to those in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study).
- Safety data through 1 month after Dose 2 from participants in each age group in Phase 2/3.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for participants in each age group in Phase 2/3.
- Complete safety and persistence-of-immunogenicity analysis after complete data are available in each age group or at the end of the study.
- Efficacy analysis across age groups for which immunobridging success is declared when at least 22 cases are accrued in these age groups.

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.

7.2. 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.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
ATC	Anatomic Therapeutic Chemical
BiPaP	bilevel positive airway pressure
BLQ	below the level of quantitation
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CVA	cerebrovascular accident
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
EU	European Union
FiO_2	fraction of inspired oxygen
GI	gastrointestinal
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HR	heart rate
ICD	informed consent document
ICU	intensive care unit
IL-6	interleukin 6
IRC	internal review committee
IRR	illness rate ratio
IVIG	intravenous immunoglobulin
IWR	interactive Web-based response
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
non-S	nonspike protein
PaO_2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
PT	preferred term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SpO_2	oxygen saturation as measured by pulse oximetry
ULN	upper limit of normal
US	United States
VE	vaccine efficacy
WHO	World Health Organization

Appendix 2. IRR and VE Derivation

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:

- 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 pain[3]

SARS-CoV-2–related hospitalization definition: confirmed COVID-19 and hospitalization.

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 9;[4]
  - SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg;

Table 9. 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 = heat 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.

- Respiratory failure (defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg):
    - <70 + (age in years × 2) for age up to 10 years, <90 + (age in years × 2) 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 baseline[5];
- Admission to an ICU;
- Death.

Confirmed MIS-C definition:[6] as per the CDC MIS-C case definition:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, acute kidney injury);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
    - Dermatologic (eg, rash, mucocutaneous lesions);
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR
- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

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

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result;

- Current or recent exposure is established by SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms;

- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

Surveillance Times

Fundamental to this VE assessment is the surveillance for cases satisfying various endpoints within each participant that may occur during the trial. Endpoint and participant combinations where surveillance is applicable require identification of the start and the end of the surveillance period in order to determine the participant-level endpoint surveillance time. For all VE-related endpoints in this study, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy	Dose 2 + 7 days
Dose 2 all-available efficacy	Dose 2 + 7 days
Dose 1 all-available efficacy	Dose 1

For all VE-related endpoints in this study, the end of a surveillance period for each participant is the earliest of the following events:

- When the first COVID-19 case occurs.

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

- When the participant has a first important protocol violation (only for analysis based on the evaluable efficacy population).

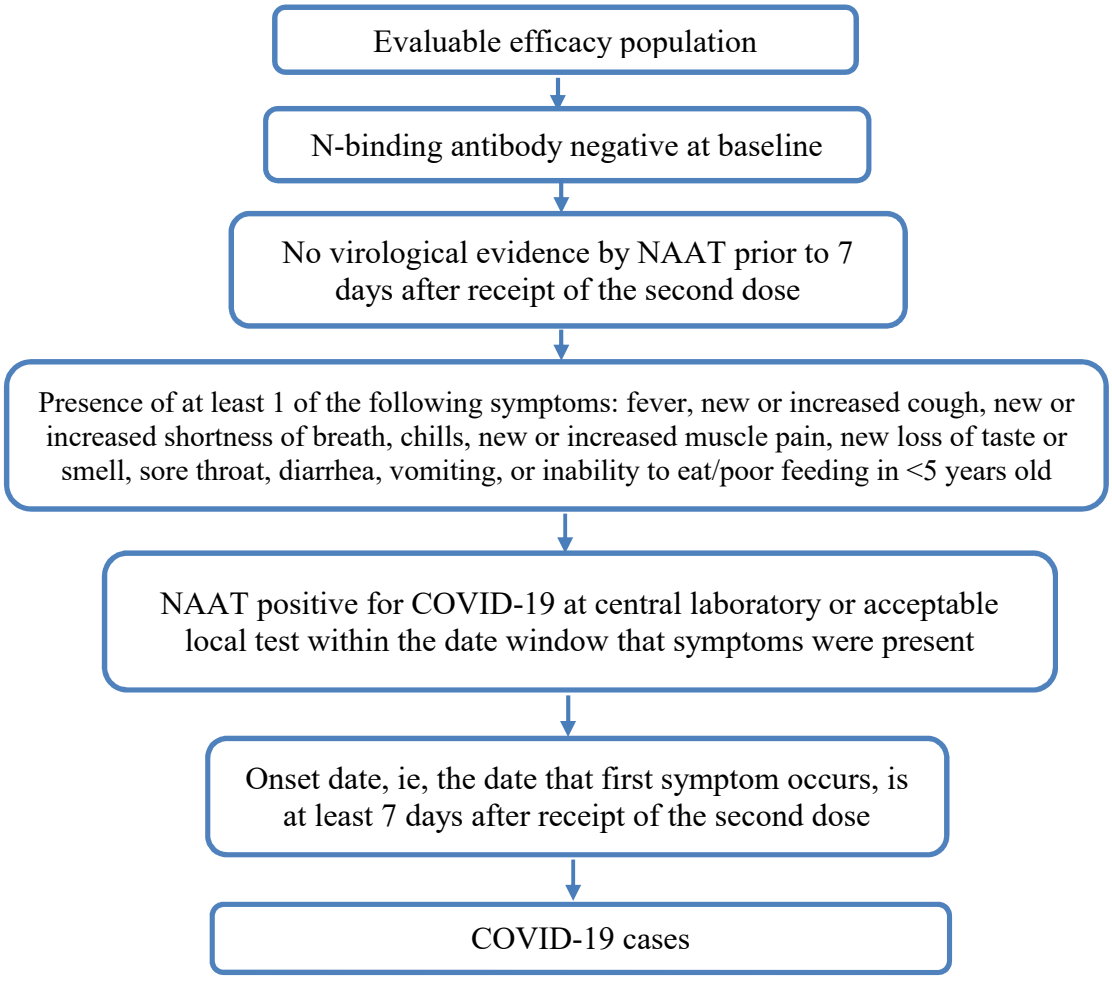
- When the participant is unblinded at the time of being eligible for receipt of BNT162b2 or other reasons.

For descriptive assessment of the COVID-19 incidence rate through the entire study follow-up period, the surveillance period is defined in the same way except that unblinding will not be considered as the end of the surveillance period.

Once the COVID-19 cases and surveillance period have been identified, VE can be calculated as $100 \times (1 - IRR)$, where IRR is the ratio of confirmed COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group.

Flowchart

1. The flowchart for deriving the COVID-19 cases included below for the VE endpoint in evaluable efficacy participants with no serological or virological evidence of past SARS-CoV-2 infection:



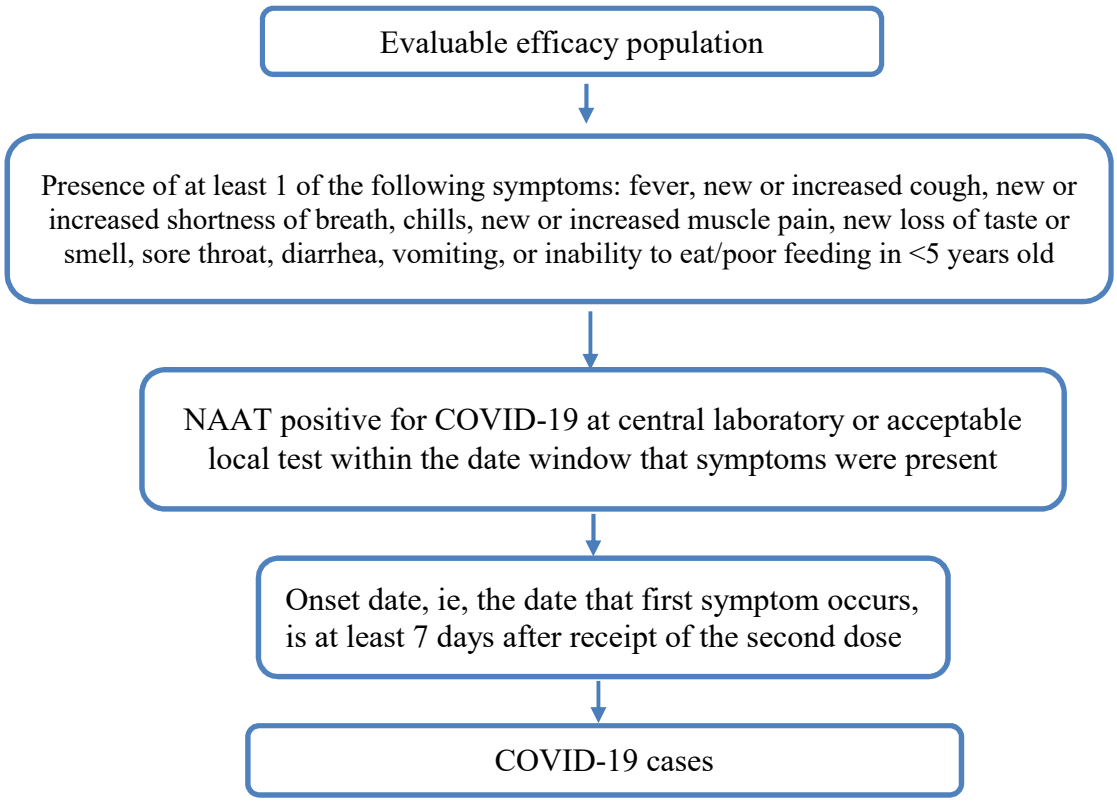
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

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

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

2. The flowchart for deriving the COVID-19 cases included below for the VE endpoint in evaluable efficacy participants with and without serological or virological evidence of past SARS-CoV-2 infection:



Appendix 3. Asymptomatic Case Based on N-Binding Antibody Seroconversion

Asymptomatic Case Definition

An asymptomatic case is defined as a positive N-binding antibody result at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT results at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2.

Surveillance Times

For the asymptomatic case based on N-binding antibody seroconversion, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy (seroconversion)	Dose 2
Dose 2 all-available efficacy	Dose 2
Dose 1 all-available efficacy	Dose 1

The end of a surveillance period for each participant is the earliest of the following events:

- Date of the first positive N-binding antibody test after Dose 2.
- Date of the participant's last post–Dose 2 N-binding antibody test that is prior to a COVID-19 symptom associated with a nonnegative NAAT result.
- Date of the participant's last post–Dose 2 N-binding antibody test that is prior to an important protocol violation (for analysis based on the evaluable efficacy population).

Protocol C4591007

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 AND YOUNG ADULTS

Statistical Analysis Plan
(SAP)

Version: 4

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
1/ 08 Apr 2021	Protocol amendment 1, 05 Mar 2021	N/A
2/ 17 Aug 2021	Protocol amendment 2, 06 Aug 2021	1. Implemented the changes made in protocol amendment 2. 2. Revised SAP title to reflect the changes in age. 3. Updated to allow an additional 2250 Phase 2/3 selected-dose participants to enlarge the size of the pediatric safety database. 4. Added Phase 1/2/3 evaluation of lower dose levels for children and young adults with corresponding objectives. 5. Added seroresponse endpoints for both Phase 2/3 selected- dose and lower-dose evaluation portions of the study.
3/ 07 Oct 2021	Protocol amendment 3, 10 Sep 2021 Protocol amendment 4, 29 Sep 2021	1. Implemented the changes made in protocol amendments 3 and 4. 2. Revised success criterion for efficacy hypotheses to a lower limit of the 95% CI of >30%. 3. Revised the required number of confirmed COVID-19 cases from 22 to 21 for efficacy analysis. 4. 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. 5. Added cell-mediated immune response in Sections 3.3 and 6.3.4. 6. Included objectives for potential troponin I testing in participants 5 to <12 and 12 to <16 years of age. 7. Revised an objective and the corresponding endpoints to describe severe COVID-19 cases in participants in the selected-dose portion of the study. 8. Added a second definition of symptoms of severe COVID-19 disease per the CDC definition. 9. Revised the calculation of age in months in Section 3.5.1.
4/ 10 Oct 2021	Protocol amendment 4, 29 Sep 2021	1. Add descriptive efficacy analysis in Section 7.1.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591007. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 2 and Table 3.

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

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × 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 populations (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will be analyzed by the all-available efficacy population. Missing laboratory results will not be imputed.

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 lower-dose age groups referred to in the objectives and estimands below are a separate cohort of participants ≥5 to <12 years, 12 to <16 years, and 16 to <30 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 of age.

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for 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	In participants receiving at least 1 dose of study intervention, the percentage of participants in each age group reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after Dose 2 • SAEs from Dose 1 to 6 months after Dose 2	Participants 16 to <30, 12 to <16, ≥5 to <12, and ≥2 to <5 years of age: • 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: • 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	In participants complying with the key protocol criteria (evaluable participants) in each age group: • GMTs at 7 days after Dose 2	• 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		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases
To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection		• Confirmed cases as per CDC criteria

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for 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, lower-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: • 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	Participants 16 to <30, 12 to <16, ≥5 to <12, and ≥2 to <5 years of age: • 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: • Local reactions (tenderness at the injection site, redness, and swelling) • Systemic events (fever, decreased appetite, drowsiness, and irritability) • AEs • SAEs
Primary Immunogenicity (Selected-Dose):	**Primary Immunogenicity (Selected-Dose):**	**Primary Immunogenicity (Selected-Dose):**
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:	• SARS-CoV-2 neutralizing titers
• 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	• 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 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[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	

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
• 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	• 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	
• 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	• 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 study	
Secondary Immunogenicity (Lower-Dose Evaluation):	**Secondary Immunogenicity (Lower-Dose Evaluation):**	**Secondary Immunogenicity (Lower-Dose Evaluation):**
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the lower dose level 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:	• SARS-CoV-2 neutralizing titers
• 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	• 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 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 ≥5 to <12 years of age and participants 16 to 25 years of age from Phase 2/3 of the C4591001 study	

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
• In participants 12 to <16 years of age compared to participants 16 to 25 years of age from Phase 2/3 of the C4591001 study	• GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants 12 to <16 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 12 to <16 years of age and participants 16 to 25 years of age from Phase 2/3 of the C4591001 study	
• In participants 16 to <30 years of age compared to participants 16 to 55 years of age from Phase 2/3 of the C4591001 study	• GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants 16 to <30 years of age to those in participants 16 to 55 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 16 to <30 years of age and participants 16 to 55 years of age from Phase 2/3 of the C4591001 study	
Secondary Immunogenicity/Efficacy (Selected-Dose):	**Secondary Immunogenicity/Efficacy (Selected-Dose):**	**Secondary Immunogenicity/Efficacy (Selected–Dose):**
To describe the immune responses elicited by prophylactic BNT162b2 at the dose level selected in each age group and persistence of immune response 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: At baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2, • GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• SARS-CoV-2 neutralizing titers

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 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:	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of blinded follow-up
• In the ≥5- to <12-year age group in the selected-dose portion of the study, if immunobridging is successful and if at least 21 cases are accrued	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
• In the ≥6-month to <2-year and ≥2- to <5-year age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
• In all age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups and if the above 2 individual age groups (≥5 to <12 years of age, ≥6 months to <2 years and ≥2 to <5 years age combined) did not accrue 21 cases	• 100 × (1 – 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 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:	• Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of blinded follow-up
• In the ≥5- to <12-year age group in the selected-dose portion of the study, if immunobridging is successful and if at least 21 cases are accrued	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
• In the ≥6-month to <2-year and ≥2- to <5-year age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
• In all age groups in the selected-dose portion of the study where immunobridging is successful, if at least 21 cases are accrued across those age groups and if the above 2 individual age groups (≥5 to <12 years of age, ≥6 months to <2 years and ≥2 to <5 years age combined) did not accrue 21 cases	• 100 × (1 – IRR) [ratio of active vaccine to placebo]	
To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection	In evaluable participants without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 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 all age groups combined	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To evaluate the immune response over time to prophylactic BNT162b2 at the dose level selected in each age group and persistence of immune response 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: At baseline and at 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2: • GMCs and/or GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2	• Full-length S-binding IgG levels and/or 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		• Confirmed severe COVID-19 cases

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands for Phase 2/3

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
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		• Confirmed cases as per CDC criteria
To describe the serological responses in Phase 2/3 participants in participants in selected-dose portion of the study to BNT162b2 at the dose level selected in each age group in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• SARS-CoV-2 neutralizing titers
To describe the safety and immunogenicity of prophylactic BNT162b2 at the dose level selected in each age group in children with stable HIV disease		• All safety and immunogenicity endpoints described above will be analyzed descriptively
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain in a subset of participants: • At baseline and at 7 days and 6 months after Dose 2		
To describe the frequency of elevated troponin I levels at baseline and after Vaccination 2 if testing is indicated based upon data accrued outside of this study		

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 ≥ 4 × LLOQ is considered seroresponse.

2.2. Study 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 <30 years of age with different dose levels assessed in each group.

Phase 1

Dose-finding evaluation: This is the open-label dose-finding portion of the study that will evaluate the 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.

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.

Lower-dose evaluation: This is the open-label lower-dose evaluation portion of the study that will evaluate the safety, tolerability, and immunogenicity of BNT162b2 on a 2-dose (separated by approximately 21 days) schedule in up to 3 age groups (participants ≥5 to <12 years, 12 to <16 years, and 16 to <30 years of age).

The purpose of the Phase 1 lower-dose evaluation is to evaluate the safety and immunogenicity of BNT162b2 from up to 2 different dose levels in each age group.

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 the Phase 2/3 lower-dose evaluation portion of the study.

Phase 2/3

Selected-dose evaluation: This 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 and 6 months after Dose 2. Immunobridging to participants 16 to 25 years of age in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and at 1, 6, 12 (original BNT162b2 group only), and 24 months after Dose 2 (original

BNT162b2 group only). In addition, efficacy against confirmed COVID-19 and against asymptomatic 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. 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. 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 have the opportunity to receive BNT162b2 (10 µg or 3 µg) based on age at the time of approval. If a participant turns 12 years of age during the study, he or she has the following 2 options: receive 10 µg within the study (following provision of informed consent) or receive a BNT162b2 30-µg dose outside of the study.

Lower-dose evaluation: This 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 lower-dose evaluation.

In this open-label study, all participants will have blood drawn at baseline prior to Dose 1 and at 1 and 6 months after Dose 2. Immunobridging to comparator participants in the C4591001 study will be based on immunogenicity data collected at baseline and 1 month after Dose 2. The persistence of the immune response will be based on immunogenicity data collected in participants at baseline and 1 and 6 months after Dose 2.

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.

Number of Participants

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 and a minimum of 32 participants per dose level (total of 160 participants) for the lower-dose evaluation.

Phase 2/3 selected-dose evaluation: This 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 9000 participants, as an additional 2250 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 will contribute to the overall analysis of the persistence of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure that this subset is representative of the whole study.

For the persistence time points of 12 and 24 months after Dose 2, approximately 70 participants from each age group in the original BNT162b2 vaccine group will have an immunogenicity blood draw in order to contribute to the analysis. All approximately 9000 participants will contribute to the VE analysis for conditional VE. Approximately 4500 participants who had post–Dose 1 blood sample collection will contribute to the asymptomatic infection analysis. 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.

Phase 2/3 lower-dose evaluation: This is the open-label 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 lower-dose evaluation, with a total of approximately 900 active participants.

Approximately 300 active participants in each age group in this phase will contribute to the immunobridging analysis at 1 month after Dose 2 and the overall analysis of the persistence of immune response at 6 months after Dose 2. These participants will be enrolled from both US and EU sites to ensure this subset is representative of the whole study.

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).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Endpoints

For participants in Phase 1 and Phase 2/3, the primary safety endpoints are as follows:

- Local reactions (redness, swelling, and pain at the injection site) for up to 7 days following each dose in each vaccine group for participants 16 to <30 years, 12 to <16 years, ≥5 to <12 years, and ≥2 to <5 years of age

- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following each dose in each vaccine group for participants 16 to <30 years, 12 to <16 years, ≥5 to <12 years, and ≥2 to <5 years of age

- Local reactions (redness, swelling, and tenderness at the injection site) for up to 7 days following each dose in each vaccine group for participants ≥6 months to <2 years of age

- Systemic events (fever, decreased appetite, drowsiness, and irritability) for up to 7 days following each dose in each vaccine group for participants ≥6 months to <2 years of age

- AEs from Dose 1 to 1 month after Dose 2

- SAEs from Dose 1 to 6 months after Dose 2

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain/tenderness at the injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 4 defines the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of each dose.

Table 4. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Dose

Variable	Yes (1)	No (0)
Presence of each local reaction on any day	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).
Presence of any local reaction on any day	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).

Note: Missing e-diary data will not be imputed. Participants with no e-diary data reported will not be included in the e-diary summaries.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in caliper units (measuring device units; range: 1 to 14 caliper units for participants <12 years of age and 1 to 20 caliper units for participants ≥12 years of age) for the first 7 days following vaccination (Days 1 through 7), and then categorized during analysis as mild, moderate, or severe using the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed for participants ≥2 years of age as absent, mild, moderate, or severe according to the grading scale in Table 5. 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 5.

Table 5. Local Reaction Grading Scale

	Participant Age	Mild (Grade 1)	Moderate (Grade 2)	Severe (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

Table 5. Local Reaction Grading Scale

	Participant Age	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life Threatening (Grade 4)[b]
	≥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 the protocol, Section 10.3.3.

For each local reaction reported for each dose, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each dose) as follows:

> maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 5), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. However, if a reaction is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing reaction would be the date/day that the next vaccine is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset Day

The onset day of each local reaction will be derived. Onset day is defined as the first day after vaccination that a reaction of any severity is reported.

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

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

3.1.1.2.1. Participants ≥2 Years of Age

The systemic events assessed and recorded in the e-diary are vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 6.

Table 6. 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
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 the protocol, Section 10.3.3.

3.1.1.2.2. Participants <2 Years of Age

The systemic events assessed and recorded in the e-diary are decreased appetite, drowsiness, and irritability; participants' parent(s)/legal guardians are to record the symptoms from Day 1 through Day 7, where Day 1 is the day of each dose. The derivations for systemic events will be handled in a way similar to the handling of local reactions with respect to presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 7.

Table 7. 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)

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 the protocol, Section 10.3.3.

3.1.1.2.3. Fever

Temperatures will be taken orally for participants ≥2 years of age, and axillary for participants <2 years of age, in the evening, daily, for 7 days following each dose (Days 1 through 7, where Day 1 is the day of each dose) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 8.

Table 8. Scale for Fever

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

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

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of each dose. For the use of antipyretic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable.

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

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

3.1.1.4. Adverse Events

AEs will be assessed from the time of informed consent through 1 month after Dose 2. AEs will be categorized according to MedDRA terms.

The primary safety endpoint “AEs from Dose 1 through 1 month after Dose 2” and other AE endpoints will be summarized by SOC and PT at the participant level for each age group.

This primary safety endpoint will be supported by summaries and listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after each dose), and AESIs (defined in Section 8.3.8 of the protocol). AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time of informed consent through approximately 6 months after Dose 2. SAEs will be categorized according to MedDRA terms.

The primary safety endpoint "SAEs from Dose 1 through 6 months after Dose 2" will be summarized by SOC and PT at the participant level for each age group.

3.1.2. Immunogenicity Endpoints

Phase 2/3 (Selected-Dose)

In participants with no serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥5 to <12 years of age compared to participants 16 to 25 years of age in Study C4591001
- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥2 to <5 years of age compared to participants 16 to 25 years of age in Study C4591001
- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥6 months to <2 years of age compared to participants 16 to 25 years of age in Study C4591001

Values below the LLOQ will be set to 0.5 × LLOQ for the analysis. The LLOQ value for neutralizing titers will be included in the analysis specification once it is available.

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

Phase 1

- SARS-CoV-2 neutralizing titers at 7 days after Dose 2

Phase 2/3 (Lower-Dose Evaluation)

In participants with no serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥5 to <12 years of age compared to participants 16 to 25 years of age in Study C4591001
- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥12 to <16 years of age compared to participants 16 to 25 years of age in Study C4591001
- SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥16 to <30 years of age compared to participants 16 to 55 years of age in Study C4591001

Phase 2/3 (Selected-Dose Evaluation)

In participants with no serological or virological evidence of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2
- Fold rises in SARS-CoV-2 neutralizing titers from baseline to each subsequent time point after Dose 2

3.2.2. Efficacy Endpoints

Phase 2/3 (Selected-Dose)

- Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection for the ≥5- to <12-year age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined, or across all age groups (if the required number of cases is not accrued in either of 2 individual age groups)
- Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection for the ≥5- to <12-year age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined, or across all age groups (if the required number of cases is not accrued in either of 2 individual age groups)
- Incidence of asymptomatic infection of SARS-CoV-2 based on N-binding antibody seroconversion in participants without serological or virological evidence of past SARS-CoV-2 infection

3.3. Exploratory Endpoints

Phase 1 (Dose-Finding)

- Confirmed COVID-19 cases
- Confirmed severe COVID-19 cases
- Confirmed MIS-C cases as per CDC criteria

Phase 2/3 (Selected-Dose)

In participants with or without serological or virological evidence of past SARS-CoV-2 infection:

- Full-length S-binding IgG levels and/or SARS-CoV-2 neutralizing titers at baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2

- Fold rises in full-length S-binding IgG levels and/or SARS-CoV-2 neutralizing titers from before Dose 1 to each subsequent time point after Dose 2

Other exploratory endpoints:

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

- Confirmed severe COVID-19 cases

- Confirmed MIS-C cases as per CDC criteria

- SARS-CoV-2 neutralizing titers by COVID-19 and SARS-CoV-2 infection status:

    - Confirmed COVID-19

    - Confirmed severe COVID-19

    - SARS-CoV-2 infection without confirmed COVID-19

- Cell-mediated immune response

- Troponin I

3.4. Other Endpoints

All safety and immunogenicity endpoints described above will be summarized separately for participants with confirmed stable HIV infection for the Phase 2/3 selected-dose portion of the study.

3.5. Baseline and Other Variables

Measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments.

3.5.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at Dose 1 (in years for participants ≥2 years of age, in months for participants ≥6 months to <2 years of age), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white, multiracial, and not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported). In cases where more than 1 category is selected for race, the category "multiracial" will be created and used for analysis. For Phase 2/3, BMI will also be included in the demographic variables for participants ≥2 years of age.

Age at Dose 1 will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 10th birthday, the participant is considered to be 9 years old. For participants ≥6 months to <2 years of age, age at Dose 1 in months will be derived as the complete calendar months between date of birth and date of Dose 1. For example, if date of birth is 25FEB2021 and date of Dose 1 is between 25AUG2021 and 24SEP2021, the participant is considered to be 6 months old. The participant is considered to be 7 months old on 25SEP2021. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of Dose 1 for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

Medical history will be categorized according to MedDRA. Comorbidities that increase the risk for severe COVID-19 illness will be categorized based on medical history terms.

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. Any findings will be recorded in the source documents and, if clinically significant, the findings will be recorded on the CRF.

3.5.2. E-Diary Transmission

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

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- Details of any nonstudy vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 5 for Phase 1 dose-finding participants and Visit 5 for Phase 2/3 selected-dose participants; Visit 105 for Phase 1 and Visit 204 for Phase 2/3 lower-dose evaluation participants; and Visit 305 for Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing participants; Visit D and Visit D1 for 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, respectively).

- 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.

- 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.

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

3.6. Safety Endpoints

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety, immunogenicity, and efficacy results in the table below. For the specified criteria in each population definition that are not associated with unblinded information (randomized vaccine or vaccine actually received), data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and the classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood sample collected within an appropriate window after Dose 2 (within 6-8 days after Dose 2 for Phase 1 and within 28-42 days after Dose 2 for Phase 2/3), 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	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
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.
Safety	All participants who receive at least 1 dose of the study intervention.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity/efficacy, eg, participant receipt of a

prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

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 over 10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the study interventions they were randomized for each age group.

The evaluable efficacy population will be the primary analysis population by each age group for all efficacy analyses. Additional analyses based on the all-available efficacy (mITT) population will be performed. Participants will be summarized according to the study interventions to which they were randomized for each age group.

The safety analyses are based on the safety population. Participants will be summarized according to the study interventions they actually received for each age group.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

For the participants in Phase 1 and in the Phase 2/3 lower-dose evaluation and 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 for Doses 1 and 2 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. Further details can be found in the protocol, Section 6.3. The timing for statistical analysis is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypothesis

The primary immunogenicity objective in Phase 2/3 is to immunobridge the immune response elicited by prophylactic BNT162b2 at the dose level selected to those of 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 and participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. The evaluable immunogenicity population will be used for testing the following hypotheses:

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

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

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) and in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study, respectively, measured 1 month after Dose 2. 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-year age group from Phase 2/3 of the C4591001 study, respectively.

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

The hypothesis related to primary objectives for each age group will be evaluated separately. Within each age group, the hypotheses 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-year 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%.

In a similar manner, the hypothesis related to the secondary objectives of the lower-dose evaluation for each age group will be evaluated separately. Within each age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially.

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 ≥ LLOQ.

5.1.2. Vaccine Efficacy Hypothesis

The secondary efficacy endpoints are to evaluate VE defined as 100 × (1 – IRR) in each of the 2 age groups (1: ≥5 to <12 years; and 2: ≥6 months to <2 years and ≥2 to <5 years combined) or across all age groups where immunobridging success is declared (if the required number of cases is not accrued in either of the 2 individual age groups) in the selected-dose portion of the study. The ≥6-month to <2-year and ≥2- to <5-year age groups 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 active vaccine group to the corresponding illness rate in the placebo group. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior infection, and VE_2 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:

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

for VE_1 and VE_2, respectively.

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

5.1.3. Multiplicity Considerations

For the immunogenicity objectives of immunobridging of BNT162b2 in each of the 5 age groups (16 to <30 years, 12 to <16 years, ≥5 to <12 years [selected-dose and lower-dose evaluation participants], ≥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 5 age groups.

Within each age group, except for the ≥5- to <12-year age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially in the order as specified. Within the ≥5- to <12-year age group, immunobridging based on GMR and seroresponse difference will be first assessed sequentially in participants from the selected-dose portion of the study, and then assessed sequentially in participants from the lower-dose evaluation portion of the study.

In each of the 2 age groups (≥5 to <12 years, ≥6 months to <2 years and ≥2 to <5 years combined) 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, VE_1 and VE_2, will be tested sequentially in the order as stated for each age group. Thus, this sequential testing strategy controls type I error at the desired level of 2.5% within each age group. Efficacy objectives for each of the 2 age groups will be assessed separately. No type I error adjustments will be applied in the efficacy assessments for the 2 age groups for the same reason described above for immunogenicity assessments. However, if the required number (21) of confirmed COVID-19 cases is not accrued in either of the 2 age groups where immunobridging success is declared, but 21 cases are accrued across all the age groups where immunobridging success is declared, then hypothesis testing will be conducted across the age groups with immunobridging success.

5.2. General Methods

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, or all age groups combined if the required number of cases is not accrued in either of the 2 individual age groups) in which immunobridging success is declared. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

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

5.2.1. Analyses for Binary Data

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

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

For Phase 2/3 only, the 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. No Tier 1 events have been identified to date for BNT162b2.

- Tier 2 events: These are events that are not Tier 1 but are considered "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 1% of participants with the AE term in at least 1 vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

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

5.2.2. Analyses for Continuous Data

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

5.2.2.1. Geometric Means

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

5.2.2.2. Geometric Mean Fold Rises

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

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

5.2.2.3. 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.

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant, following the Pfizer standard of handling incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

The LLOQ for each assay will be provided by Vaccine Research and Development as part of the electronic data transfer or within the Clinical Testing Completion Memo prior to statistical analysis. Assay results above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. However, this calculation may be adjusted based upon additional data from the assay. LLOQ results will be included in the analysis specification once they are available.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands:
  - The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose in participants 16 to <30 years, 12 to <16 years, ≥5 to <12 years, and ≥2 to <5 years of age for Phase 1 and Phase 2/3 participants in each portion of the study (Section 2.1).
  - The percentage of participants reporting local reactions (redness, swelling, and tenderness at the injection site) within 7 days after each dose in participants ≥6 months to <2 years of age for Phase 1 and Phase 2/3 participants in each portion of the study (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each and any local reaction after each dose in each vaccine group per age group will be presented by maximum severity and cumulatively across severity levels. Confirmed e-diary errors will be excluded from the analysis. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplemental Analyses

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

- Duration (days) of each local reaction after each dose.

- Onset day of each local reaction after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group per age group.

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

Figures:

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

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimands:
  - The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, new or worsened joint pain) within 7 days after each dose in participants 16 to <30 years, 12 to <16 years, ≥5 to <12 years and ≥2 to <5 years of age for Phase 1 and Phase 2/3 participants in each portion of the study (Section 2.1).
  - The percentage of participants reporting systemic events (fever, decreased appetite, drowsiness, and irritability) within 7 days after each dose in participants ≥6 months to <2 years of age for Phase 1 and Phase 2/3 participants in each portion of the study (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group per age group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analyses

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

- Duration of each systemic event after each dose.
- Onset day of each systemic event after each dose.

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum for each vaccine group per age group.

The use of antipyretic medication (see Section 3.1.1.3) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

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

Figures:

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

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 2 for Phase 1 and Phase 2/3 participants in each portion of the study (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 1 month after Dose 2.
- Analysis methodology: Descriptive statistics for Phase 1 and Phase 2/3, 3-tiered approach for the Phase 2/3 selected-dose portion (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of AEs from Dose 1 through 1 month after Dose 2 will be provided for each vaccine group per age group. For both Tier 1 (if any) and Tier 2 events, the between-group difference in proportions and the associated 95% CI based on the Miettinen and Nurminen[2] method will be provided. For Tier 1 events (if any), the asymptotic p-values for the difference in

proportions will be provided. For Tier 3 events, counts and percentages will be provided for each vaccine group per age group.

6.1.1.3.2. Supplemental Analyses

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

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

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 1 through 6 months after Dose 2 for Phase 1 and Phase 2/3 participants in each portion of the study (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 6 months after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 through 6 months/1 month after Dose 2 will be provided for each vaccine group per age group.

6.1.2. Immunogenicity Endpoint (Phase 2/3 Selected-Dose)

6.1.2.1. 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

6.1.2.1.1. Main Analyses

- Estimands:
  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥2 to <5 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥6 months to <2 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after Dose 2.

- Analysis methodology: The GMRs and associated 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be the younger age group minus the group 16 to 25 years of age. Immunobridging success will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8 (Section 5.2.2.3).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence of past SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.

- Reporting results: The GMRs and associated 2-sided 95% CIs will be provided.

- Estimands:

  - The difference in percentages of participants with seroresponse in participants ≥5 to <12 years of age and the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

  - The difference in percentages of participants with seroresponse in participants ≥2 to <5 years of age and the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

  - The difference in percentages of participants with seroresponse in participants ≥6 months to <2 years of age and the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after Dose 2.

- Analysis methodology: The differences in percentages of participants with seroresponse will be provided along with associated 2-sided 95% CIs calculated using the Miettinen and Nurminen[2] method (Section 5.2.1). 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 greater than -10%.

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence of past SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.

- Reporting results: Counts, percentages of participants with seroresponse, the difference in percentages, and the associated 2-sided 95% CIs will be provided.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoint (Phase 1)

6.2.1.1. SARS-CoV-2 Neutralizing Titers

6.2.1.1.1. Main Analyses

- Estimand: GMTs (Section 2.1).

- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time points: 7 Days after Dose 2.

- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1.

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

- Reporting results: GMTs and 2-sided 95% CIs will be provided for each vaccine group per age group before vaccination and at each subsequent time point after vaccination.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers at each time point by vaccine group per age group.

6.2.2. Immunogenicity Endpoint (Phase 2/3 Lower-Dose Evaluation)

6.2.2.1. SARS-CoV-2 Neutralizing Titers in Participants ≥5 to <12 Years, ≥12 to <16 Years, and 16 to 30 Years of Age to Those 16 to 25 Years or 16 to 55 Years of Age in Study C4591001

6.2.2.1.1. Main Analyses

- Estimands:
  - GMR of the SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).
  - The difference in percentages of participants with seroresponse in participants ≥5 to <12 years of age and the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).
  - GMR of the SARS-CoV-2 neutralizing titers in participants 12 to <16 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).
  - The difference in percentages of participants with seroresponse in participants 12 to <16 years of age and the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).
  - GMR of the SARS-CoV-2 neutralizing titers in participants 16 to <30 years of age to those in the 16- to 55-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).
  - The difference in percentages of participants with seroresponse in participants 16 to <30 years of age and the 16- to 55-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: The GMRs and associated 2-sided 95% CI will be derived in the same way as for the primary endpoints in Section 6.1.2.1.1. The differences in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints in Section 6.1.2.1.1.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence of past

SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.

- Reporting results: The GMRs and associated 2-sided 95% CIs will be provided. Counts, percentages of participants with seroresponse, the difference in percentages, and the associated 2-sided 95% CIs will be provided.

6.2.3. Immunogenicity Endpoint (Phase 2/3 Selected-Dose)

6.2.3.1. SARS-CoV-2 Neutralizing Titers for Participants Without Evidence of Past SARS-CoV-2 Infection

6.2.3.1.1. Main Analyses

- Estimands:
  - GMTs in participants with no serological or virological evidence of past SARS-CoV-2 infection (Section 2.1).
  - GMFRs from before Dose 1 to each subsequent time point after Dose 2 in participants with no serological or virological evidence of past SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time points: Baseline (before Dose 1) and 1, 6, 12 (for the original BNT162b2 group only), and 24 (for the original BNT162b2 group only) months after Dose 2.
- Analysis methodology: GMTs and the associated 2-sided CIs will be derived as described in Section 5.2.2.1. GMFRs and the associated 2-sided CIs will be calculated as described in Section 5.2.2.2.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. Only participants with no serological or virological evidence of past SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.
- Reporting results: GMTs and 2-sided 95% CIs will be provided for each vaccine group per age group before vaccination and at each subsequent time point after Dose 2. GMFRs and 2-sided 95% CIs will be provided for each vaccine group per age group from before vaccination to each subsequent time point after Dose 2.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers at each time point for each vaccine group per age group.

6.2.4. Vaccine Efficacy Endpoints (Phase 2/3 Selected-Dose)

6.2.4.1. COVID-19 Incidence per 1000 Person-Years of Blinded Follow-up

6.2.4.1.1. Main Analyses

- Estimands:
  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants without evidence of past SARS-CoV-2 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 and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined, or across all age groups (if the required number of cases is not accrued in either of 2 individual age groups) (Section 2.1)].
  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants with or without evidence of past SARS-CoV-2 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 and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined, or across all age groups (if the required number of cases is not accrued in either of 2 individual age groups) (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).
- Analysis methodology: Assessment of VE will be performed for confirmed COVID-19 illness (using the first definition in Appendix 2) from 7 days after Dose 2, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group (see Appendix 2 for details on the derivation of IRR and VE). The hypothesis test for the VE objective will be performed if at least 21 cases are accrued at the time of analyses.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided for the corresponding age groups.

6.2.4.1.2. Supplemental Analyses

The same assessment of VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time for the corresponding age groups will be performed for confirmed COVID-19 illness based on CDC-defined symptoms (using the second definition in Appendix 2).

6.2.4.2. Incidence of Asymptomatic Infection of SARS-CoV-2 Based on N-Binding Antibody Seroconversion in Participants Without Evidence of Past SARS-CoV-2 Infection

6.2.4.2.1. Main Analyses

- Estimand: 100 × (1 - IRR) [ratio of asymptomatic infection based on the N-binding antibody seroconversion per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection for the active vaccine group to the placebo group (Section 2.1)].

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

- Analysis time point: End of the surveillance period.

- Analysis methodology: Assessment of VE will be performed for the incidence of asymptomatic infection of SARS-CoV-2, and will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of incidence of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection rate in the placebo group (see Appendix 3 for details on the definition of asymptomatic infection and the derivation of IRR and VE).

- Intercurrent events and missing data: Missing N-binding data will not be imputed.

- Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided for pooled age groups where immunobridging success is declared.

6.3. Exploratory Endpoints

6.3.1. Immunogenicity Endpoints (Phase 2/3 Selected-Dose)

6.3.1.1. Main Analyses

- GMCs of full-length S-binding IgG levels and/or GMTs of SARS-CoV-2 neutralizing titers along with GMFRs will be summarized for each vaccine group per age group in participants with or without serological or virological evidence of past SARS-CoV-2 infection using the same statistical analysis method described for the secondary immunogenicity endpoints.

- GMTs and GMFRs of SARS-CoV-2 neutralizing titers will be summarized for each vaccine group per age group in each subset of participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19 using the same statistical analysis methods described for the secondary immunogenicity endpoints.

6.3.2. Vaccine Efficacy Endpoints (Phase 2/3 Selected-Dose)

6.3.2.1. Main Analyses

- Estimand: 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants without, and with and without, evidence of past SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group (Section 2.1).

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

- Analysis time point: End of the surveillance period (blinded follow-up).

- Analysis methodology: 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 participant is 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 (detailed separately, and available in the electronic study reference portal). Descriptive summary of VE and the associated 2-sided 95% CI will be derived using same method as in Section 6.2.4.1.1.

- Intercurrent events and missing data: Missing data will not be imputed.

- Reporting results: VE and the associated Clopper-Pearson 95% CI for confirmed COVID-19 illness (using the first definition in Appendix 2) from 7 days after Dose 2 through the blinded follow-up period will be provided for each age group and across all age groups by including additional follow-up data during the blinded follow-up or at the end of the blinded follow-up period.

6.3.2.2. Supplemental Analyses

The same assessment of VE and the associated Clopper-Pearson 95% CI will be performed for confirmed COVID-19 illness (using the second definition in Appendix 2).

6.3.3. COVID-19 Cases

6.3.3.1. Main Analyses

- Estimands:

  Phase 1 (Dose-Finding)

  - Confirmed COVID-19 cases (Section 2.1).
  - Confirmed severe COVID-19 cases (Section 2.1).
  - Confirmed MIS-C cases as per CDC criteria (Section 2.1).

  Phase 2/3 (Selected-Dose)

  - Confirmed severe COVID-19 cases (Section 2.1).
  - Confirmed MIS-C cases as per CDC criteria (Section 2.1).

- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of confirmed severe COVID-19 cases (using the first definition in Appendix 2) and confirmed MIS-C cases as per CDC criteria will be provided.

6.3.3.2. Supplemental Analyses

The same analyses will be performed for confirmed severe COVID-19 (using the second definition in Appendix 2).

6.3.4. Cell-Mediated Immune Response

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 at baseline and at 7 days and 6 months after Dose 2.

6.3.5. Troponin I

Counts and percentages of participants with elevated troponin I level at baseline and after Vaccination 2 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.

6.4. Other Endpoints

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively for Phase 2/3.

AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 or no later than at the ~6-month post–Dose 2 visit.

6.5. Subset Analyses

For Phase 2/3, subgroup analyses based on sex, race, and ethnicity will be performed on all primary safety and immunogenicity endpoints (as supplemental analyses).

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

6.6.1.1. Demographic Characteristics

Demographic characteristics, including age at Dose 1, sex, race, ethnicity, and classification of BMI for participants ≥2 years of age, will be summarized for the safety population for each vaccine group and overall per age group.

6.6.1.2. Medical History

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

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccinations (Doses 1 and 2), who completed the study, and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment) per age group. The reasons for withdrawal will be those as specified in the database.

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

6.6.2.2. Blood Samples for Assay

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

6.6.2.3. Transmission of E-Diaries

The participants who were vaccinated and have completed e-diaries after each dose will be summarized according to the vaccine actually received. The summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for each dose according to the vaccine actually received per age group.

The safety population will be used.

6.6.3. Study Vaccination Exposure

6.6.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for randomized participants in Phase 1 and the Phase 2/3 selected-dose (original and safety expansion) evaluation, lower-dose evaluation, and obtaining-serum-samples-for-potential-troponin I-testing portions of the study. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall per age group.

In addition, the relation of randomized vaccine to vaccine actually received will be presented as a cross tabulation of the vaccine actually received versus the randomized vaccine per age group.

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

6.6.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. All vaccines received within 28 days before Dose 1 will be listed. The number and percentage of participants receiving each concomitant vaccine after Dose 1 will be tabulated by vaccine group per age group. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.7. Safety Summaries and Analyses

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs, are described under the Primary Endpoints (see Section 6.1).

7. 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.

7.1. Analysis Timings

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 or approximately 300 participants in the Phase 2/3 lower-dose evaluation 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).

- 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, lower-dose evaluation, or obtaining-serum-samples-for-potential-troponin I-testing portions of the study.

- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for participants in each age group in the Phase 2/3 selected-dose or lower-dose evaluation portions 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 persistence-of-immunogenicity 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 or 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 are accrued in these age groups or efficacy analysis across all age groups for which immunobridging success is declared when at least 21 cases are accrued across all 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.

A descriptive efficacy analysis in the ≥5- to <12-year age group will be conducted to provide available efficacy data (in addition to the completed immunogenicity and safety analyses

described above) to facilitate VRBPAC's overall assessment of benefit-risk when the EUA for this age group is being considered. With less than 21 cases accrued by the time of this analysis, there is an increased risk of observing by chance a lower vaccine efficacy than the true vaccine efficacy compared to the same risk when 21 or more cases have been accrued. In order to inform VRBPAC's decision on whether to recommend approving the vaccine for this age group, an important issue for public health policy decision makers, Pfizer will provide the most comprehensive and up-to-date data available, despite the potential risk of a higher 'type II error' for this descriptive efficacy analysis.

7.2. 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.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
ATC	Anatomic Therapeutic Chemical
BiPaP	bilevel positive airway pressure
BLQ	below the level of quantitation
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CVA	cerebrovascular accident
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
EU	European Union
FiO_2	fraction of inspired oxygen
GI	gastrointestinal
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HR	heart rate
ICD	informed consent document
ICU	intensive care unit
IgG	immunoglobulin G
IL-6	interleukin 6
IRC	internal review committee
IRR	illness rate ratio
IVIG	intravenous immunoglobulin
IWR	interactive Web-based response
LDH	lactate dehydrogenase

Abbreviation	Term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
non-S	nonspike protein
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
PT	preferred term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SpO_2	oxygen saturation as measured by pulse oximetry
ULN	upper limit of normal
US	United States
VE	vaccine efficacy
WHO	World Health Organization

Appendix 2. IRR and VE Derivation

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:

- 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 pain[3];
- Lethargy.

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 9[4]; SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg);

Table 9. 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.

- Respiratory failure (defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg):
    - <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or requiring vasoactive drugs to maintain BP in the normal range;
- Significant acute renal failure: Serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine;
- Significant GI/hepatic failure: 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 baseline[5];

- 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,[6] as per the CDC MIS-C case definition:

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, acute kidney injury);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism);
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia);
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea);
    - Dermatologic (eg, rash, mucocutaneous lesions);
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR

- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

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

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: Positive N-binding antibody result in a participant with a prior negative N-binding antibody result;

- Current or recent exposure is established by SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms;

- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

Surveillance Times

Fundamental to this VE assessment is the surveillance for cases satisfying various endpoints within each participant that may occur during the trial. Endpoint and participant combinations where surveillance is applicable require identification of the start and the end of the surveillance period in order to determine the participant-level endpoint surveillance time. For all VE-related endpoints in this study, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy	Dose 2 + 7 days
Dose 2 all-available efficacy	Dose 2 + 7 days
Dose 1 all-available efficacy	Dose 1

For all VE-related endpoints in this study, the end of a surveillance period for each participant is the earliest of the following events:

- When the first COVID-19 case occurs.

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

- When the participant has a first important protocol violation (only for analysis based on the evaluable efficacy population).

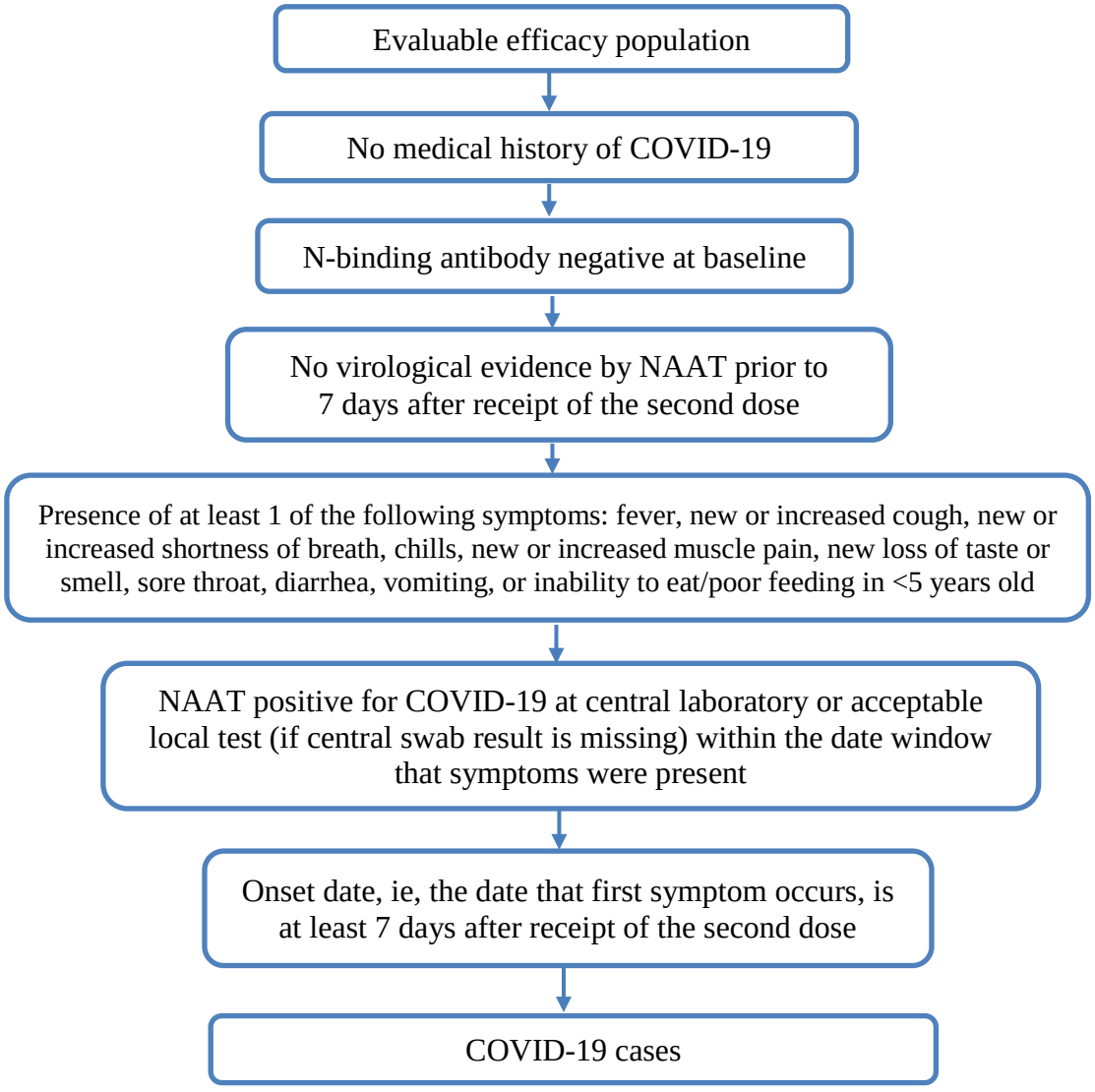
- When the participant is unblinded at the time of being eligible for receipt of BNT162b2 or other reasons.

For descriptive assessment of the COVID-19 incidence rate through the entire study follow-up period, the surveillance period is defined in the same way except that unblinding will not be considered as the end of the surveillance period.

Once the COVID-19 cases and surveillance period have been identified, VE can be calculated as 100 × (1 – IRR), where IRR is the ratio of confirmed COVID-19 illness per 1000 person-years of follow-up for the active vaccine group to the placebo group.

Flowchart

1. The flowchart for deriving the COVID-19 cases included below for the VE endpoint in evaluable efficacy participants with no serological or virological evidence of past SARS-CoV-2 infection:



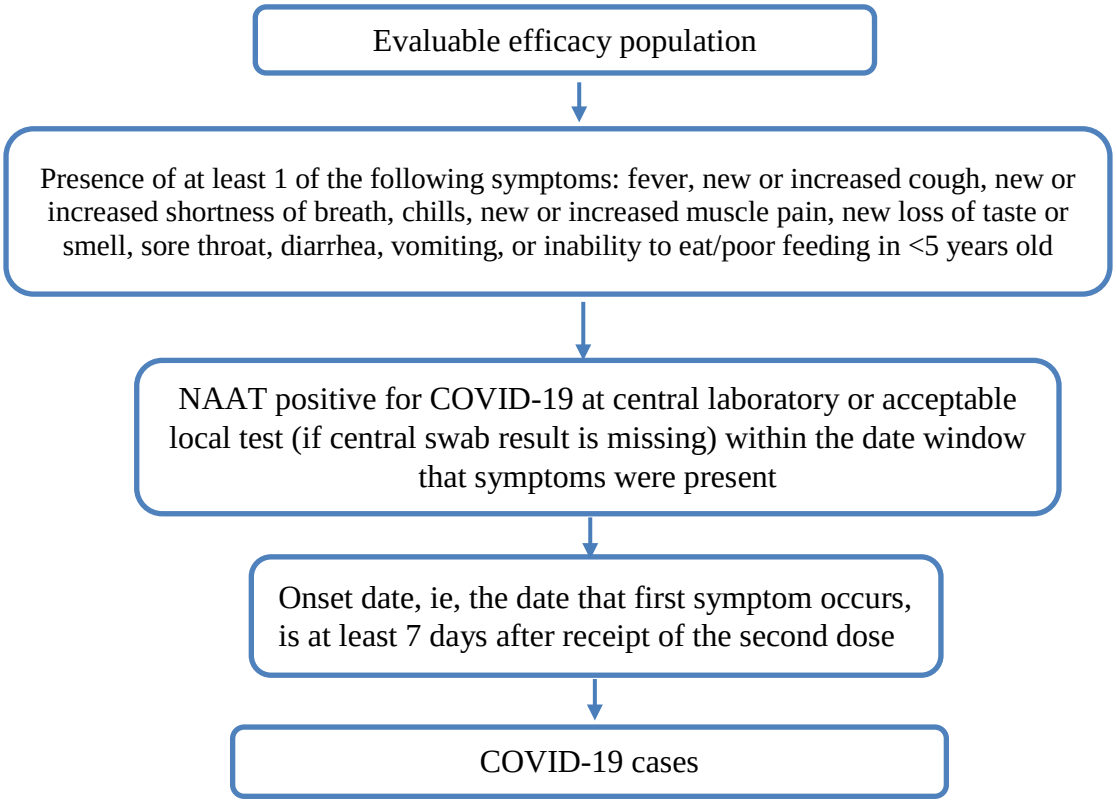
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

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

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

2. The flowchart for deriving the COVID-19 cases included below for the VE endpoint in evaluable efficacy participants with and without serological or virological evidence of past SARS-CoV-2 infection:



Appendix 3. Asymptomatic Case Based on N-Binding Antibody Seroconversion

Asymptomatic Case Definition

An asymptomatic case is defined as a positive N-binding antibody result at a post–Dose 2 visit in participants without medical history of COVID-19 or serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT results at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2.

Surveillance Times

For the asymptomatic case based on N-binding antibody seroconversion, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy (seroconversion)	Dose 2
Dose 2 all-available efficacy	Dose 2
Dose 1 all-available efficacy	Dose 1

The end of a surveillance period for each participant is the earliest of the following events:

- Date of the first positive N-binding antibody test after Dose 2.
- Date of the participant's last post–Dose 2 N-binding antibody test that is prior to a COVID-19 symptom associated with a nonnegative NAAT result.
- Date of the participant's last post–Dose 2 N-binding antibody test that is prior to an important protocol violation (for analysis based on the evaluable efficacy population).