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

Statistical Analysis Plan
(SAP)

Version: 6

Date: 11 Jul 2023

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APPENDICES

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.
5/ 29 Mar 2022	Protocol amendment 5, 15 Nov 2021	1. Implemented the changes made in protocol amendments 5. 2. Removed ≥5 to <12 years of age from Lower Dose Evaluation cohort. 3. Revised age range for the oldest age group to ≥16 to <18 years of age in Lower Dose Evaluation cohort. 4. Revised Phase 1/2/3 dose schedule for Lower Dose Evaluation cohort. 2. Included an exploratory objective to describe the immune response to emerging VOCs.
	Protocol amendment 6, 04 Jan 2022	1. Implemented the changes made in protocol amendments 6. 2. Added corresponding objectives, estimands, and endpoints associated with an additional (third) dose of BNT162b2 for all Phase 1 dose-finding and Phase 2/3 selected-dose participants. 3. An additional 4500 Phase 2/3 selected-dose participants ≥6 months to <2 years and ≥2 to <5 years of age are permitted to enroll to enlarge the size of the pediatric safety database.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
	Protocol amendment 7, 10 Mar 2022	1. Implemented the changes made in protocol amendments 7. 2. Clarified that the dose interval for Phase 2/3 selected-dose participants enrolled in the ≥2 to <5 years age group who originally received placebo and will turn 5 years of age prior to crossing over to active vaccine will be the same as for the ≥5 to <12 years age group (ie, third dose administered at least 6 months after the second dose). 3. Added a relative VE objective for 3-dose BNT162b2 from original active vaccine group vs 2-dose BNT162b2 from placebo crossover. 4. Revised the objective for troponin I with an additional (third) dose of BNT162b2 at least 5 months after Dose 2 to all Phase 2/3 participants enrolled to support obtaining serum samples for potential troponin I testing.
6/ 11 Jul 2023	Protocol amendment 8, 28 Apr 2023	1. Implemented the changes made in protocol amendment 8. 2. Removed corresponding sections and wording throughout the SAP text for the lower-dose evaluation. 3. Removed secondary/exploratory objectives with corresponding text throughout the SAP: o To describe the efficacy of prophylactic BNT162b2 against asymptomatic infection in participants ≥5 to <12 years age in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection. o To describe the immune responses elicited by prophylactic BNT162b2 at the selected dose level at varying intervals between Dose 2 and Dose 3 in the selected-dose portion of the study. o To describe the serological responses in Phase 2/3 participants in the selected-dose portion of the study to BNT162b2 at the dose level selected in each age group in cases of: • Confirmed COVID-19 with and without coinfection • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19 4. Added an exploratory objective to describe the incidence of confirmed COVID-19 through the entire study follow-up period. o Added corresponding estimands, endpoints, and statistical analysis methods. 5. Removed appendix 3.

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 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 • AEs from Dose 3 to 1 month after Dose 3 • SAEs from Dose 3 to 6 months after Dose 3	Participants ≥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 each time point	• 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 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 • AEs from Dose 3 to 1 month after Dose 3 • SAEs from Dose 3 to 6 months after Dose 3	Participants ≥12 to <16, ≥5 to <12, and ≥2 to <5 years of age: • 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 2-Dose Series):	**Primary Immunogenicity (Selected-Dose 2-Dose Series):**	**Primary Immunogenicity (Selected-Dose 2-Dose Series):**
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in each age group and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection:	• 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[a] 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[a] 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.	
Primary Immunogenicity (Selected-Dose 3-Dose Series):	**Primary Immunogenicity (Selected-Dose 3-Dose Series):**	**Primary Immunogenicity (Selected-Dose 3-Dose Series):**
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in each age group and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 3) of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection:	• SARS-CoV-2 neutralizing titers
• 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 at 1 month after Dose 3 in participants ≥2 to <5 years of age to those at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. • The difference in percentages of participants with seroresponse[a] at 1 month after Dose 3 in participants ≥2 to <5 years of age and at 1. month after Dose 2 in	

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

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
	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 at 1 month after Dose 3 in participants ≥6 months to <2 years of age to those at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study. • The difference in percentages of participants with seroresponse[a] at 1 month after Dose 3 in participants ≥6 months to <2 years of age and at 1 month after Dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study.	
Secondary Immunogenicity/Efficacy (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 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: • GMTs at each time point. • GMFRs from before Dose 1 to each subsequent time point after Dose 2 or Dose 3.	• SARS-CoV-2 neutralizing titers
Secondary Efficacy (Selected-Dose 2-Dose Series):	**Secondary Efficacy (Selected-Dose 2-Dose Series):**	**Secondary Efficacy (Selected-Dose 2-Dose Series):**
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 to prior to Dose 3 during the blinded follow-up period in participants in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection:	• Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 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]	

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 to prior to Dose 3 during the blinded follow-up period in participants in the selected-dose portion of the study with or without evidence of past SARS-CoV-2 infection:	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection:	• Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 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]	
Secondary Efficacy (Selected-Dose 3-Dose Series):	**Secondary Efficacy (Selected-Dose 3-Dose Series):**	**Secondary Efficacy (Selected-Dose 3-Dose Series):**
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥6 months to <5 years of age in the selected-dose portion of the study without evidence of past SARS-CoV-2 infection.	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection: 100 × (1 - IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥6 months to <5 years of age in the selected-dose portion of the study with or without evidence of past SARS-CoV-2 infection.	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection: 100 × (1 - IRR) [ratio of active vaccine to placebo]	• Confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 to prior to Dose 3 during the blinded follow-up period in participants in the selected-dose portion of the study without, and with and without, evidence of past SARS-CoV-2 infection in each age group and in ≥6 months to <2 years and ≥2 to <5 years age groups combined.	In participants complying with the key protocol criteria (evaluable participants) after receipt of the second dose of study intervention: 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 describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥6 months to <5 years of age in the selected-dose portion of the study	In participants complying with the key protocol criteria (evaluable participants) after receipt of the third dose of study intervention:	• COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT

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

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
without, and with and without, evidence of past SARS-CoV-2 infection in each age group.	100 × (1 - IRR) [ratio of active vaccine to placebo]	
To describe the relative VE of prophylactic BNT162b2 against confirmed COVID-19 illness from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 during the same calendar time interval of interest. Participants from the original active vaccine group receiving 3 doses of BNT162b2 will be compared to participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding in each age group and the ≥6-month to <2-year and ≥2- to <5-year age groups combined.	In all participants from the original active vaccine group receiving 3 doses of BNT162b2 and participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding: 100 × (1 - IRR) [ratio of original active vaccine to placebo crossover]	• COVID-19 incidence per 1000 person-years based on central laboratory or locally confirmed NAAT
To evaluate the immune response elicited by prophylactic BNT162b2 at the dose level selected in each age group in Phase 2/3 participants with and without serological or virological evidence of past SARS-CoV-2 infection.	In evaluable participants with or without serological or virological evidence of past SARS-CoV-2 infection from each vaccine group: • GMCs and/or GMTs at each time point • GMFRs from before Dose 1 to each subsequent time point after Dose 2 or Dose 3	• 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
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 immune response to emerging VOCs.		• SARS-CoV-2 neutralizing titers for VOCs

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

Phase 2/3		
Objectives	**Estimands**	**Endpoints**
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain in a subset of participants.		
To describe the frequency of elevated troponin I levels at baseline and after Vaccination 2 and/or 3 if testing is indicated based upon data accrued outside of this study.		
To describe the SARS-CoV-2 lineage distribution among participants as determined by next-generation sequencing.		
To describe the incidence of confirmed COVID-19 during the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently.	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

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

2.2. Study Design

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

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

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 schedule (separated by approximately 21 days) in 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 this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose.

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

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

Phase 2/3

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

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

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

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

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

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

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

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

As of protocol amendment 8, the study will be concluded early, following agreement with the FDA and EMA, for 2 reasons: (1) The study is now fully unblinded with no control arm, making it observational in nature. (2) There is increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. Following approval of protocol amendment 8, active study participants will be informed of the early completion of the study and further data collection will cease 6 months after the third dose of BNT162b2.

Number of Participants

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

Phase 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 13,500 participants, as an additional 4500 participants will be included to further enlarge the size of the pediatric safety database. Participants will be randomized in a 2:1 ratio to receive active vaccine or placebo.

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

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

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

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

Among participants ≥6 months to <2 years and ≥2 to <5 years of age enrolled after protocol amendment 6, approximately 300 participants (200 in the active vaccine group and 100 in the placebo group) randomized in each age group will have an immunogenicity blood draw at 1 month after Dose 3 and approximately 100 participants in the original BNT162b2 group will have an immunogenicity blood draw at 6, 12, and 18 months after Dose 3 (As of 20 October 2022, a blood sample is no longer required at 6, 12, and 18 months after Dose 3. The objective to assess the persistence of the immune response is removed in protocol amendment 8).

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 ≥12 to <16 years (Phase 2/3 troponin participants only), ≥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 ≥12 to <16 years (Phase 2/3 troponin participants only), ≥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.
- AEs from Dose 3 to 1 month after Dose 3.
- SAEs from Dose 3 to 6 months after Dose 3.

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 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 tenderness at the injection site
Redness	<12 Years	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device unit) = >2.0 to 7.0 cm	>14 caliper units (or measuring device unit) = >7 cm	Necrosis or exfoliative dermatitis
	≥12 Years	5 to 10 caliper units (or measuring device units) = >2.0 to 5.0 cm	11 to 20 caliper units (or measuring device units) = >5.0 to 10.0 cm	>20 caliper units (or measuring device units) = >10 cm	Necrosis or exfoliative dermatitis
Swelling	<12 Years	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
	≥12 Years	5 to 10 caliper units (or measuring device units) = >2.0 cm to 5.0 cm	11 to 20 caliper units (or 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 and from Dose 3 through 1 month after Dose 3. AEs will be categorized according to MedDRA terms.

The primary safety endpoints "AEs from Dose 1 through 1 month after Dose 2 and "AEs from Dose 3 through 1 month after Dose 3" 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 (prior to Dose 3) and from Dose 3 through 6 months after Dose 3. SAEs will be categorized according to MedDRA terms.

The primary safety endpoints "SAEs from Dose 1 through 6 months after Dose 2 (prior to Dose 3) and "SAEs from Dose 3 through 6 months after Dose 3" 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 2-Dose Series)

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 those at 1 month after Dose 2 in 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 those at 1 month after Dose 2 in 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 those at 1 month after Dose 2 in participants 16 to 25 years of age in Study C4591001.

Phase 2/3 (Selected-Dose 3-Dose Series)

In participants with no serological or virological evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection:

- SARS-CoV-2 neutralizing titers at 1 month after Dose 3 in participants ≥2 to <5 years of age compared to those at 1 month after Dose 2 in participants 16 to 25 years of age in Study C4591001.
- SARS-CoV-2 neutralizing titers at 1 month after Dose 3 in participants ≥6 months to <2 years of age compared to those at 1 month after Dose 2 in 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 each time point.

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 each time point.

- Fold rises in SARS-CoV-2 neutralizing titers from baseline to each subsequent time point after Dose 2 or Dose 3.

3.2.2. Efficacy Endpoints

Phase 2/3 (Selected-Dose 2-Dose Series)

- Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 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.

- Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 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.

Phase 2/3 (Selected-Dose 3-Dose Series)

- Confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up in participants without serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection for the ≥6-month to <2-year and ≥2- to <5-year age groups combined.

- Confirmed COVID-19 incidence from 7 days after Dose 3 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 3) of past SARS-CoV-2 infection for the ≥6-month to <2-year and ≥2- to <5-year age groups combined.

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:

- SARS-CoV-2 neutralizing titers at each time point.

- Fold rises in SARS-CoV-2 neutralizing titers from before Dose 1 to each subsequent time point after Dose 2 or Dose 3.

Other exploratory endpoints:

- COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT for each age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined.

- COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT for each of the ≥6 months to <2 years and ≥2 to <5 years age groups.

- COVID-19 incidence from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 per 1000 person-years of the same calendar time interval of interest based on central laboratory or locally confirmed NAAT for each age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined.

- Confirmed severe COVID-19 cases.

- Confirmed MIS-C cases as per CDC criteria.

- Immune response to emerging VOCs.

- Cell-mediated immune response.

- Troponin I.

- SARS-CoV-2 Lineage Distribution.

- COVID-19 incidence through the entire study follow-up period per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT for participants in each group who received BNT162b2 at initial randomization or subsequently.

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 and Visit 5C for Phase 1 dose-finding participants and Visit 5 and Visit X for Phase 2/3 selected-dose participants who originally received BNT162b2; Visit 305 for Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing participants; Visit F and Visit 105 for Phase 2/3 selected-dose participants who originally received placebo; and Visit F1 for Phase 2/3 obtaining-serum-samples-for-potential-troponin I-testing [≥5 to <12 years old] participants who originally

received placebo only; Visit 405 for Phase 2/3 selected-dose participants ≥6 months to <5 years of age enrolled from protocol amendment 6 onwards; Visit E105 for Phase 2/3 selected-dose participants ≥6 months to <5 years of age enrolled from protocol amendment 6 onwards who originally received placebo).

- Prohibited medications (not intended to treat COVID-19/MIS-C illness) listed in Section 6.5.1 of the protocol will be recorded in the prohibited medication CRF.

- Prohibited COVID-19 vaccinations listed in Section 6.5.1 of the protocol will be recorded in the concomitant vaccination CRF.

- Any prescribed medication to treat, or intended to treat, COVID-19/MIS-C illness, including receipt of antiplatelets (eg, aspirin, clopidogrel) or anticoagulants (eg, heparin, enoxaparin, warfarin), will be recorded in the concomitant medication CRF within the COVID-19 illness visit.

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 (2-dose)	All eligible randomized participants who receive 2 doses of the vaccine with the same dose level to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1 for 21-day interval, within 51-61 days after Dose 1 for 8-week interval in the lower-dose evaluation portion), 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
Evaluable immunogenicity (3-dose)	All eligible randomized participants who receive 3 doses of the vaccine with the same dose level to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1 for 21-day interval, within 51-61 days after Dose 1 for 8-week interval in the lower-dose evaluation portion), with Dose 3 received within the predefined window (at least 175 days after Dose 2 for ≥5- to <12-year age group and the participants in the ≥2- to <5-year age group turning 5 years of age prior to crossing over, at least 60 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled before Protocol Amendment 6, within 54-70 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled after Protocol Amendment 6), have at least 1 valid and determinate immunogenicity result after Dose 3 from the blood sample collected within an appropriate window after Dose 3 (within 28-42 days after Dose 3), and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	Dose 2 all-available immunogenicity: All randomized participants who receive 2 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2 from the blood sample collected at 1 month after Dose 2 visit regardless of visit window. Dose 3 all-available immunogenicity: All randomized participants who receive 3 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 3.
Evaluable efficacy (2-dose)	All eligible randomized participants who receive 2 doses of the vaccine with the same dose level to which they are 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 before 7 days after Dose 2.
Evaluable efficacy (3-dose)	All eligible randomized participants who receive 3 doses of the vaccine with the same dose level to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), with Dose 3 received within the predefined window (at least 175 days after Dose 2 for ≥5- to <12-year age group and the participants in the ≥2- to <5-year age group turning 5 years of age prior to crossing over, at least 60 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled before Protocol Amendment 6, within 54-70 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled after Protocol Amendment 6), and have no other important protocol deviations as determined by the clinician before 7 days after Dose 3.
All-available efficacy (mITT)	Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination. Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses. Dose 3 all-available efficacy: All randomized participants who complete 3 vaccination doses.
Safety	All participants who receive at least 1 dose of the study intervention.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is one 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 a 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 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 or 1 month after Dose 3 (≥2 to <5 years and ≥6 months to <2 years of age) and participants 16 to 25 years of age at 1 month after Dose 2 from Phase 2/3 of the C4591001 study. The evaluable immunogenicity population will be used for 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) measured 1 month after Dose 2 (or Dose 3) and in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study measured 1 month after Dose 2, respectively. For the seroresponse endpoint, p_2 and p_1 are the (true) proportions of participants achieving seroresponse in each younger age group and the 16- to 25-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 greater than -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, all 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 (≥5 to <12 years: after 2-dose series; ≥6 months to <2 years and ≥2 to <5 years combined: after 3-dose series) in the selected-dose portion of the study. The ≥6 months to <2 years and ≥2 to <5 years are combined for the VE evaluation because the same dose level was selected for these 2 age groups. Age groups in which immunobridging is not shown to be successful will not be included in the VE evaluation. IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group.

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

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

In the ≥5- to <12-year age group in the selected-dose portion of the study, where immunobridging success is declared, if the required number (21) of confirmed COVID-19 cases is accrued, then the secondary VE objectives, VE_1 and VE_2, will be tested sequentially in the order as stated. Thus, this sequential testing strategy controls type I error at the desired level of 2.5%.

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

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) 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 ≥12 to <16 years (Phase 2/3 troponin participants only), ≥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 of 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 ≥12 to <16 years (Phase 2/3 troponin participants only), ≥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 of 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 and AEs from Dose 3 through 1 month after Dose 3 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, Dose 3 through 1 month after Dose 3.

- 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 and AEs from Dose 3 through 1 month after Dose 3 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 (prior to Dose 3) and SAEs from Dose 3 through 6 months after Dose 3 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 (prior to Dose 3), Dose 3 through 6 months after Dose 3.

- 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 (prior to Dose 3) and SAE from Dose 3 through 6 months after Dose 3 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:

  2-Dose Series

  - GMR of the SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥5 to <12 years of age to those at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥2 to <5 years of age to those at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants ≥6 months to <2 years of age to those at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (Section 2.1).

  3-Dose Series

  - GMR of the SARS-CoV-2 neutralizing titers at 1 month after Dose 3 in participants ≥2 to <5 years of age to those at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection (Section 2.1).

  - GMR of the SARS-CoV-2 neutralizing titers at 1 month after Dose 3 in participants ≥6 months to <2 years of age to those at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection (Section 2.1).

- Analysis set: Evaluable immunogenicity (2-dose) population for 2-dose series, evaluable immunogenicity (3-dose) population for 3-dose series, and all-available immunogenicity populations (as applicable) (Section 4).

- Analysis time point: 1 Month after Dose 2 for 2-dose series, 1 Month after Dose 3 for 3-dose series.

- Analysis methodology: Only participants enrolled prior to protocol amendment 6 will contribute to 3-Dose immunobridging analysis. 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 nonnegative NAAT or N-binding result.

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

- Estimands:

  2-Dose Series

  - The difference in percentages of participants with seroresponse at 1 month after Dose 2 in participants ≥5 to <12 years of age and at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (Section 2.1).

  - The difference in percentages of participants with seroresponse at 1 month after Dose 2 in participants ≥2 to <5 years of age and at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (Section 2.1).

  - The difference in percentages of participants with seroresponse at 1 month after Dose 2 in participants ≥6 months to <2 years of age and at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (Section 2.1).

  3-Dose Series

  - The difference in percentages of participants with seroresponse at 1 month after Dose 3 in participants ≥2 to <5 years of age and at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection (Section 2.1).

  - The difference in percentages of participants with seroresponse at 1 month after Dose 3 in participants ≥6 months to <2 years of age and at 1 month after Dose 2 in the 16- to 25-year age group in Study C4591001 for participants without evidence (up to 1 month after receipt of Dose 3 or Dose 2, as appropriate) of past SARS-CoV-2 infection (Section 2.1).

- Analysis set: Evaluable immunogenicity (2-dose) population for 2-dose series, evaluable immunogenicity (3-dose) population for 3-dose series, and all-available immunogenicity populations (as applicable) (Section 4).

- Analysis time point: 1 Month after Dose 2 for 2-dose series, 1 Month after Dose 3 for 3-dose series.

- Analysis methodology: Only participants enrolled prior to protocol amendment 6 will contribute to 3-Dose immunobridging analysis. 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 nonnegative NAAT or 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 (2-dose) population, evaluable immunogenicity (3-dose) population, and all-available immunogenicity populations (as applicable) (Section 4).

- Analysis time points: Each time point.

- 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 Selected-Dose)

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 or Dose 3 in participants with no serological or virological evidence of past SARS-CoV-2 infection (Section 2.1).
- Analysis set: Evaluable immunogenicity (2-dose) population, evaluable immunogenicity (3-dose) population, and all-available immunogenicity populations (as applicable) (Section 4).
- Analysis time points: Each time point.
- 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 nonnegative NAAT or 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 or Dose 3. 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 or Dose 3.

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 Selected-Dose)

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

6.2.3.1.1. Main Analyses

- Estimands:

  2-Dose Series

  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up in participants without evidence of 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 (Section 2.1)].

  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up in participants with 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 (Section 2.1)].

  3-Dose Series

  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 3 per 1000 person-years of blinded follow-up in participants without evidence of past SARS-CoV-2 infection (prior to 7 days after receipt of Dose 3) for the active vaccine group to the placebo group for the ≥6-month to <2-year and ≥2- to <5-year age groups combined (Section 2.1)].

  - 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 3 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 3) for the active vaccine group to the placebo group for the ≥6-month to <2-year and ≥2- to <5-year age groups combined (Section 2.1)].

- Analysis set: Evaluable efficacy (2-dose) population for 2-dose series, evaluable efficacy (3-dose) population for 3-dose series, 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 to prior to Dose 3 (≥5 to <12 years of age) or from 7 days after Dose 3 (≥6 months to <2 years and ≥2 to <5 years of age combined), 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 in the specific age groups (≥5 to <12 years; ≥6 months to <2 years and ≥2 to <5 years combined) in which immunobridging is shown to be successful.

- 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.

6.2.3.1.2. 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 the corresponding age groups will be performed for confirmed COVID-19 illness based on CDC-defined symptoms (using the second definition in Appendix 2).

6.3. Exploratory Endpoints

6.3.1. Immunogenicity Endpoints (Phase 2/3 Selected-Dose)

6.3.1.1. Main Analyses

- 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.

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 to prior to Dose 3 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 for each age group and for the ≥6 months to <2 years and ≥2 to <5 years age groups combined (Section 2.1).

- 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 3 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 3) for the active vaccine group to the placebo group for each of the ≥6 months to <2 years and ≥2 to <5 years age groups (Section 2.1).

- 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 per 1000 person-years of the same calendar time interval of interest in participants from the original active vaccine group receiving 3 doses of BNT162b2 to participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding for each age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined (Section 2.1).

- Incidence rate of confirmed COVID-19 illness through the entire study follow-up period per 1000 person-years of follow-up for participants in each age group who received BNT162b2 at initial randomization or subsequently (Section 2.1).

- Analysis set: Evaluable efficacy (2-dose) population, Evaluable efficacy (3-dose) population, 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 for the ≥5- to <12- year age group (detailed separately, and available in the electronic study reference portal). The 2 younger age groups will receive Dose 3 and continue blinded follow-up after Dose 3. Descriptive summary of VE and the associated 2-sided 95% CI will be derived using same method as in Section 6.2.3.1.1.

- 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 to prior to Dose 3 through the blinded follow-up period will be provided for each age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined by including additional follow-up data during the blinded follow-up or at the end of the blinded follow-up period.

  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 3 during the blinded follow-up period will be provided for each of the ≥6-month to <2-year and ≥2- to <5-year age groups.

  VE and the associated Clopper-Pearson 95% CI for confirmed COVID-19 illness (using the first definition in Appendix 2) confirmed COVID-19 illness from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 during the same calendar time interval of interest may be provided. Participants from the original active vaccine group receiving 3 doses of BNT162b2 will be compared to participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding for each age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined.

  Incidence rate (per 1000 person-years of follow-up) and 2-sided 95% CI for confirmed COVID-19 illness after receipt of each dose of BNT162b2 will be provided for participants in each age group who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.

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). Descriptive analysis of VE may be conducted for regulatory purposes prior to the required number of cases being accrued for the secondary VE hypotheses to facilitate overall assessment of benefit-risk by regulatory authorities.

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 (2-dose) population, evaluable efficacy (3-dose) population, and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Listings.
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Listings 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. Immune Response to Emerging VOCs

GMTs and/or GMFRs of SARS-CoV-2 VOC-neutralizing titers, along with the associated 2-sided 95% CIs, will be provided at specific time points for each vaccine group. GMRs of SARS-CoV-2 VOC-neutralizing titers to reference-strain neutralizing titers may also be calculated along with the associated 2-sided 95% CIs.

6.3.5. 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.

6.3.6. Troponin I

Counts and percentages of participants with elevated troponin I level at baseline and after Vaccination 2 and/or 3 will be provided if testing is indicated based upon data accrued outside of this study. The associated Clopper-Pearson 95% CIs will also be provided.

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 after the first dose of BNT162b2 will be summarized separately for participants who originally received placebo and then received BNT162b2 after unblinding.

Participants who aged up in the study and received different dose levels at Dose 2 and/or Dose 3 will be summarized separately.

6.5. Subset Analyses

For Phase 2/3, subgroup analyses based on sex, race, ethnicity, and baseline SARS-CoV-2 status 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 included in the immunobridging analysis in each age group (immunobridging analysis of SARS-CoV-2 neutralizing titers in each age group compared to the comparator group from Phase 2/3 of the C4591001 study).
- Immunogenicity data through 1 month after Dose 3 from the approximately 300 participants in the Phase 2/3 selected-dose portion of the study included in the immunobridging analysis in each of the 2 younger age groups (immunobridging analysis of SARS-CoV-2 neutralizing titers in the ≥6-month to <2-year and ≥2- to <5-year age groups compared to the comparator group from Phase 2/3 of the C4591001 study).
- Safety data through 1 month after Dose 2 from participants ≥5 to <12 years of age in the Phase 2/3 selected-dose portion of the study enrolled before safety expansion.
- Safety data through 1 month after Dose 2 from all participants in each age group in the Phase 2/3 selected-dose evaluation or obtaining-serum-samples-for-potential-troponin I-testing portions of the study.
- Safety data through 1 month after Dose 3 from all participants in each age group in the Phase 2/3 selected-dose portion of the study.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for participants in each age group in the Phase 2/3 selected-dose 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 immunogenicity analysis approximately 6 months after Dose 3 for participants in each age group in the Phase 2/3 selected-dose portions of the study.
- Complete safety analysis after complete data are available in each age group or at the end of the study.

- Efficacy analysis in the ≥5- to <12-year age group when immunobridging success is declared and at least 21 cases are accrued from 7 days after Dose 2 to prior to Dose 3.

- Efficacy analysis in the ≥6-month to <2-year and ≥2- to <5-year age groups combined for which immunobridging success is declared when at least 21 cases from 7 days after Dose 3 are accrued in these age groups.

- Updated efficacy analysis at the end of the blinded follow-up period.

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

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

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
CVA	cerebrovascular accident
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
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
IWR	interactive Web-based response
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation

Abbreviation	Term
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
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
VOC	variant of concern

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.

COVID-19 Cases Without Coinfection of Other Pathogens

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

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

- Clinical signs at rest indicative of severe systemic illness (RR [breaths/min] and HR [beats/min] as shown in Table 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.
Note: It is anticipated that HR and RR measurements would be obtained from medical records generated as part of the participant's standard of care. Efforts should be made to measure HR and RR when the participant is not crying or anxious, and measurements should be repeated as needed to ensure an accurate and reliable measurement. Only measurements considered clinically significant by the investigator should be reported in the CRF. Document the attempts in the source and reflect the consistent measurement in the CRF.

- Respiratory failure (defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg):

- <70 + (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; all positive RT-PCR cases confirmed by the central laboratory will undergo BioFire testing.
- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

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 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 (3-dose)	Dose 3 + 7 days
Evaluable efficacy (2-dose)	Dose 2 + 7 days
Dose 3 all-available efficacy	Dose 3 + 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:

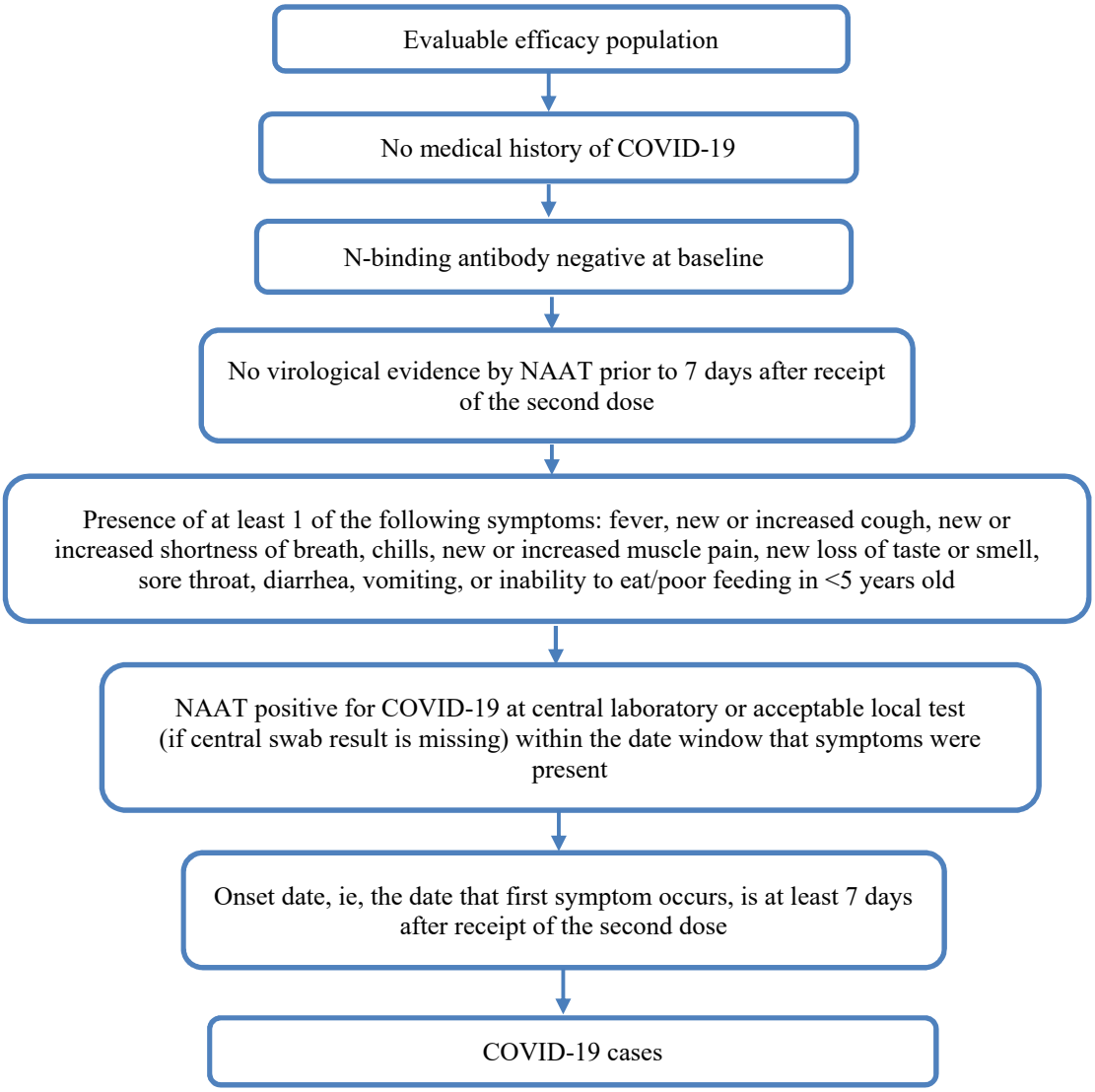
- When the first COVID-19 case occurs.
- When the participant's end of the study occurs due to, eg, withdrawal or death or trial completion, etc.
- When the participant has a first important protocol violation (only for analysis based on the evaluable efficacy population).
- When the participant is unblinded at the time of being eligible for receipt of BNT162b2 or other reasons.
- When the participant received the 3rd dose of BNT162b2 or placebo (only for VE analysis prior to Dose 3).

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 is for the VE endpoint in evaluable efficacy (dose-2) participants from 2-Dose series with no serological or virological evidence of past SARS-CoV-2 infection. The flowchart for evaluable efficacy (dose-3) participants in 3-Dose series can be similarly derived:



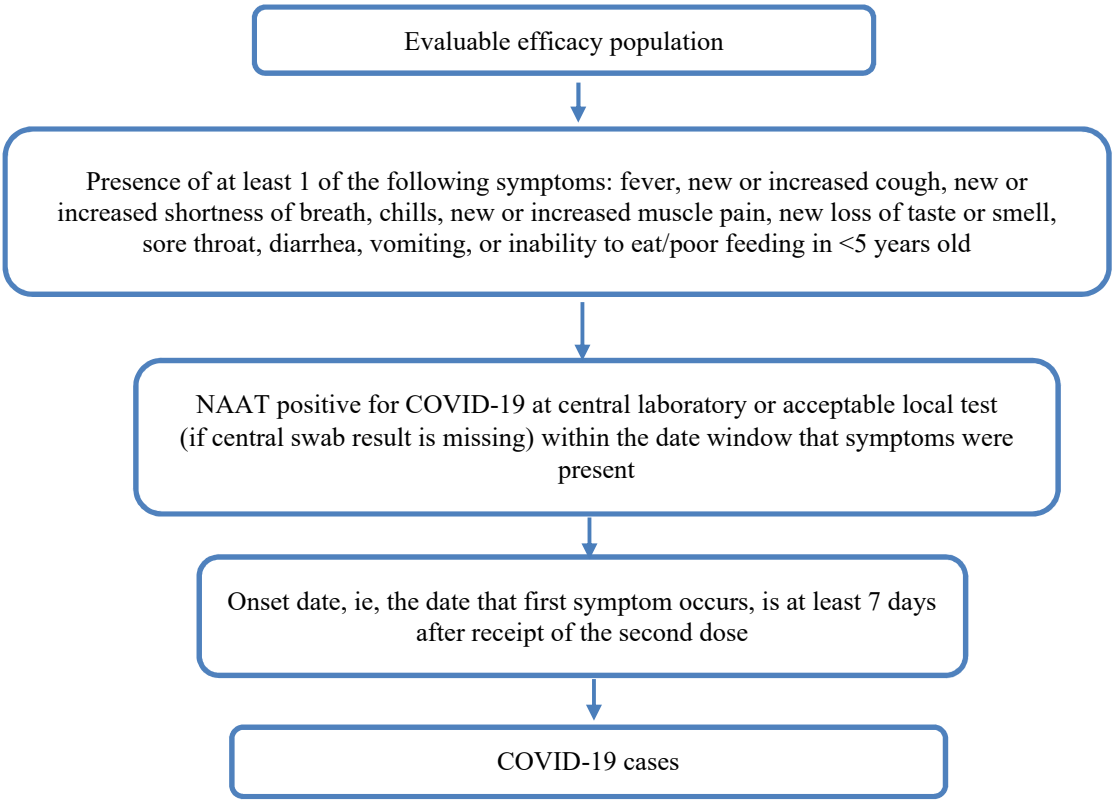
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

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 is for the VE endpoint in evaluable efficacy (2-dose) participants from 2-dose series with and without serological or virological evidence of past SARS-CoV-2 infection. The flowchart for evaluable efficacy (3-dose) participants from 3-dose series can be similarly derived:



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