Protocol C4591001

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Statistical Analysis Plan
(SAP)

Version: 5

Date: 17 Mar 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Summary and Rationale for Changes
1/ 20 May 2020	Protocol amendment 1, 13 May 2020	N/A
2/ 30 Jul 2020	Protocol amendment 5, 24 July 2020	Implemented the changes made in protocol amendments 2 through 5.
3/ 02 Nov 2020	Protocol amendment 9, 29 Oct 2020	Implemented the changes made in protocol amendments 6 through 9.
4/ 08 Jan 2021	Protocol amendment 11, 04 Jan 2021	Implemented the changes made in protocol amendments 10 and 11.
5/ 17 Mar 2021	Protocol amendment 14, 02 Mar 2021	Implemented the changes made in protocol amendments 12 through 14.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591001. 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 tertiary/exploratory objective are described in Table 2 and Table 3 below.

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

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity (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 antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy (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 populations. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

Table 2. List of Primary and Secondary Objectives, Estimands, and Endpoints for Phase 1

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in the protocol, Section 10.2
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	SARS-CoV-2 neutralizing titers
	• Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination	S1-binding IgG levels and RBD-binding IgG levels

Table 2. List of Primary and Secondary Objectives, Estimands, and Endpoints for Phase 1

Objectives	Estimands	Endpoints
	• Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point	• SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune responses elicited by a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	• GMC/GMT at the time of Dose 3 and 7 days and 1 month after Dose 3, and GMFR from before Dose 3 to 7 days and 1 month after Dose 3	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers • Full-length S-binding or S1-binding IgG levels
	• GMR of SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 3 to 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers
	• GMR of SARS-CoV-2 SA-variant neutralizing titers 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers 1 month after Dose 2	• SARS-CoV-2 reference-strain neutralizing titers • SARS-CoV-2 SA-variant neutralizing titers
To describe the safety profile of a third dose of prophylactic BNT162b2 administered to healthy adults 6 to 12 months after the second dose of either BNT162b1 or BNT162b2	In participants receiving a third dose of BNT162b2, the percentage of participants reporting: • Local reactions for up to 7 days after Dose 3 • Systemic events for up to 7 days after Dose 3 • AEs and SAEs from Dose 3 to 1 month after Dose 3	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

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

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days 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 follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection

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

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days 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 follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety and tolerability profile of BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants, or as 2 doses to BNT162b2-naïve participants To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2-experienced participants	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 5 or 6 months after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

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

Objectives[a]	Estimands	Endpoints
Primary Immunogenicity *BNT162b2-experienced participants*		
To demonstrate the noninferiority of the anti–reference strain immune response after a third dose of BNT162b2 compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after the third dose of BNT162b2 to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
BNT162b2-naïve participants		
To demonstrate the noninferiority of the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to the anti–reference strain immune response after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days 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 follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days 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 follow-up based on central laboratory or locally confirmed NAAT

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

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days 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 follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) • at least 7 days and • at least 14 days 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 follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19

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

Objectives[a]	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
BNT162b2-experienced participants		
To demonstrate the noninferiority of the anti-SA immune response after a third dose of BNT162b2 compared to the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the third dose of BNT162b2 to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the third dose of BNT162b2) of past SARS-CoV-2 infection
To demonstrate the noninferiority of the anti–reference strain immune response after 1 dose of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2, in the same individuals	GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 1 dose of BNT162b2$_{SA}$ and a third dose of BNT162b2	GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the third dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and 1 month after the third dose of BNT162b2	SARS-CoV-2 SA NT in participants with no serological or virological evidence (up to 1 month after receipt of 1 dose of BNT162b2$_{SA}$ or the third dose of BNT162b2) of past SARS-CoV-2 infection
To descriptively compare the anti-SA immune response after 2 doses of BNT162b2$_{SA}$ and the anti–reference strain immune response after 2 doses of BNT162b2, in the same individuals	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second	SARS-CoV-2 SA and reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$) of past SARS-CoV-2 infection

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

Objectives[a]	Estimands	Endpoints
	dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2	
BNT162b2-naïve participants		
To demonstrate a statistically greater anti-SA immune response after 2 doses of BNT162b2$_{SA}$ compared to after 2 doses of BNT162b2	GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 SA NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
To descriptively compare the anti–reference strain immune response after 2 doses of BNT162b2$_{SA}$ and after 2 doses of BNT162b2	GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2	SARS-CoV-2 reference strain NTs in participants with no serological or virological evidence (up to 1 month after receipt of the second dose of BNT162b2$_{SA}$ or BNT162b2 as appropriate) of past SARS-CoV-2 infection
Exploratory		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination	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 incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently	In participants who received BNT162b2 (at initial randomization or subsequently): 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
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT and GMFR at baseline and 1, 6, 12, and 24 months after completion of vaccination	• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers

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

Objectives[a]	Estimands	Endpoints
To describe the incidence of non-S seroconversion to SARS-CoV-2 through the entire study follow-up period in participants who received BNT162b2 at initial randomization	In participants who received BNT162b2 at initial randomization: Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the serological responses to the BNT vaccine candidate and characterize the SARS-CoV-2 isolate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• Full-length S-binding or S1-binding IgG levels • SARS-CoV-2 neutralizing titers • Identification of SARS-CoV-2 variant(s)
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2"[b]		• AEs • SAEs • SARS-CoV-2 neutralizing titers
To describe the immune response to any VOCs not already specified	Geometric mean NT for any VOCs not already specified, after any dose of BNT162b2$_{SA}$ or BNT162b2	• SARS-CoV-2 NTs for any VOCs not already specified

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

Objectives[a]	Estimands	Endpoints
To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain and SA in a subset of participants: • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 1 or 2 doses to BNT162b2-experienced participants • 7 Days and 1 and 6 months after BNT162b2$_{SA}$ given as 2 doses to BNT162b2-naïve participants • 7 Days and 1 and 6 months after BNT162b2 given as a third dose to BNT162b2-experienced participants		

a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
b. See the protocol, Section 6.1.1, for description of the manufacturing process.

2.2. Study Design

2.2.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (see protocol, Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

In order to describe the boostability of BNT162, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity. The assessment of boostability will be further expanded in a subset of Phase 3 participants who will receive a third dose of BNT162b2 or a third and potentially a fourth dose of prototype BNT162b2$_{VOC}$ (based upon the South African variant and hereafter referred to as BNT162b2$_{SA}$). To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2$_{SA}$ given as a 2-dose series, separated by 21 days.

2.2.2. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see protocol, Section 8.2).
- Controlled enrollment (required only for the first candidate and/or dose level studied):
  - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day.
  - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions.
  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
- Application of stopping rules.

- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
    - Escalation between dose levels will be based on IRC review of at least 7-day post–Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01).
    - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC.

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post–Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

Participants who originally received placebo and become eligible for receipt of BNT162b2 or another COVID-19 vaccine according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 1 placebo recipient who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than at the approximate time participants in Phase 2/3 reach Visit 4.

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (protocol, Section 1.3.3).

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2.

Phase 1 participants who originally received BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg at Doses 1 and 2 will be offered an additional dose of BNT162b2 at 30 µg approximately 6 to 12 months after their second dose of BNT162.

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

2.2.3. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 μg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of ≥60%, after the second dose of study intervention, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE >30% with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 280 participants from each of the 2 age groups

(12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing "Process 1" will be selected for this descriptive analysis.

For evaluation of boostability and protection against emerging VOCs, 600 existing Phase 3 participants 18 to 55 years of age will be rerandomized in a 1:1 ratio to receive either a third dose of BNT162b2 or a third dose of BNT162b2$_{SA}$.

An additional group of 30 existing Phase 3 participants 18 to 55 years of age will be enrolled to receive a third and fourth dose of BNT162b2$_{SA}$. For these 30 participants, through 1 month after their first dose of BNT162b2$_{SA}$ the participants will be blinded to their vaccine allocation, but the investigator and sponsor will not be. Serum samples from these participants may be used for assay development purposes and, except for objectives relating to response to a fourth dose, their results will be analyzed separately from the main immunogenicity analyses.

Three hundred participants 18 to 55 years of age who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19 will be enrolled as a new cohort of participants to receive BNT162b2$_{SA}$ given as a 2-dose series.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Participants ≥16 years of age who originally received placebo and become eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will have the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator will ensure the participant meets at least 1 of the recommendation criteria.

Any Phase 2/3 placebo recipient ≥16 years of age who has not already been offered the opportunity to receive BNT162b2 will be given this opportunity no later than 6 months after Vaccination 2 (at the time of the originally planned Visit 4).

Any participant who originally received placebo but then goes on to receive BNT162b2 will move to a new visit schedule (protocol, Section 1.3.3).

The changes to the protocol as part of protocol amendment 14 to assess boostability and homologous/heterologous protection against emerging VOCs allow the evaluation of safety and immunogenicity of BNT162b2$_{SA}$:

- When given as a third dose to C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously (ie, BNT162b2-experienced) and have not experienced COVID-19.

- In a small separate group of individuals who previously received 2 doses of BNT162b2 followed by 1 dose of BNT162b2$_{SA}$, a second BNT162b2$_{SA}$ dose will also be given 1 month after Dose 1 of BNT162b2$_{SA}$.

- When given as a 2-dose series, separated by 21 days, in newly recruited participants who are COVID-19 vaccine–naïve (ie, BNT162b2-naïve) and have not experienced COVID-19.

In addition, a group of C4591001 Phase 3 participants who received a second dose of BNT162b2 approximately 6 months previously will receive a third dose of BNT162b2.

This approach will allow an evaluation of immunogenicity against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected South African VOC, using a noninferiority approach based on neutralizing antibody titers in prior BNT162b2 vaccinees who receive either a homologous boost (with BNT162b2) or a heterologous boost (with BNT162b2$_{SA}$), as well as new vaccinees receiving 2 doses of BNT162b2$_{SA}$.

An intensive period of surveillance to evaluate the efficacy of BNT162b2 against asymptomatic SARS-CoV-2 infection may be conducted at selected sites among Phase 2/3 participants following approval of protocol amendment 11. After an initial in-person visit where a blood sample will be collected and a nasal (midturbinate) swab obtained, nasal (midturbinate) swabs will be obtained from consented participants every 2 weeks until Visit 4, or a sufficient number of cases of SARS-CoV-2 infection have accrued to evaluate this objective, whichever is sooner, per the SoA in the protocol, Section 1.3.6. The swabs will be tested at a central laboratory using NAAT to detect SARS-CoV-2. Participants who are unblinded because they become potentially eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, will not participate in surveillance for asymptomatic SARS-CoV-2 infection. However, participants who provided additional consent to conduct biweekly swabbing for surveillance of asymptomatic infection should continue to swab even after unblinding if they originally received BNT162b2.

Surveillance for asymptomatic SARS-CoV-2 infection (swabbing) should cease in participants enrolled into the subset of participants who will receive an additional dose of BNT162b2 or BNT162b2$_{SA}$.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Endpoints

For all participants in Phase 1, a subset of at least 6000 participants randomized in Phase 2/3, receiving at least 1 dose of study intervention, BNT162b2-experienced participants receiving 1 or 2 doses of BNT162b2$_{SA}$, BNT162b2-naïve participants receiving 2 doses of BNT162b2$_{SA}$, and BNT162b2-experienced participants receiving the third dose of BNT162b2 in Phase 3, below are the primary safety endpoints for local reactions and systemic events:

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each dose in each vaccine group.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose in each vaccine group.

For all participants randomized in Phase 1 and Phase 2/3, receiving at least 1 dose of study intervention, below are the primary safety endpoints for AEs and SAEs (the last dose in Phase 1 is the second dose):

- AEs from Dose 1 to 1 month after the second dose.
- SAEs from Dose 1 to 6 months after the second dose.

In addition, for the first 360 participants randomized in Phase 2/3 (Phase 2 portion), receiving at least 1 dose of study intervention, below are the primary safety endpoints for AEs and SAEs:

- AEs from Dose 1 to 7 days after the second dose.
- SAEs from Dose 1 to 7 days after the second dose.

Last, for the BNT162b2-experienced participants receiving 1 or 2 doses of BNT162b2$_{SA}$, BNT162b2-naïve participants receiving 2 doses of BNT162b2$_{SA}$, and BNT162b2-experienced participants receiving the third dose of BNT162b2 in Phase 3, below are the primary safety endpoints for AEs and SAEs:

- AEs from Dose 1 to 1 month after the last dose.
- SAEs from Dose 1 to 5 or 6 months after the last dose.

3.1.1.1. Local Reactions

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

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 for each dose, where Day 1 is the day of each dose, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7);
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

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

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

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for each and any of the local reactions (redness, swelling, and pain at the injection site) and for each and any of the severe local reactions within the interval from Day 1 through Day 7 after each dose.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading 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 by the participant as absent, mild, moderate, or severe according the grading scale in Table 5.

Table 5. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity.	Interferes with activity.	Prevents daily activity.	Emergency room visit or hospitalization for severe pain.
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units).	>5.0 cm to 10.0 cm (11 to 20 measuring device units).	>10 cm (≥21 measuring device units).	Necrosis or exfoliative dermatitis.
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units).	>5.0 cm to 10.0 cm (11 to 20 measuring device units).	>10 cm (≥21 measuring device units).	Necrosis.

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 of reporting any severity.

For the onset day of each local reaction, if participants report 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)

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 way local reactions are handled for presence of event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.1.1). Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 7 for summary of maximum temperature.

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe fatigue.
Chills	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe chills.
New or worsened muscle pain	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe new or worsened muscle pain.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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.

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

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

Table 7. Scale for Fever

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

Note: Fever is defined as 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 the second dose or 1 month after the last dose for the subset for evaluation of boostability and protection against emerging VOCs.

The primary endpoints "AEs from Dose 1 to 1 month after the second dose" and "AEs from Dose 1 to 1 month after the last dose," for evaluation of boostability and protection against emerging VOCs, and other AE endpoints will be summarized by SOC and PT at the participant level. For the subset for evaluation of boostability and protection against emerging VOCs, Dose 1 refers to the first dose of BNT162b2$_{SA}$ or first dose of BNT162b2 booster.

These primary endpoints will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose).

AE reporting will be based on the specific reporting period. Standard algorithms for handling missing AE dates will be applied as described in the Pfizer Vaccine data standard rules.

For Phase 2/3 only, a 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.
- 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% 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.

3.1.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the second dose of study intervention (Visit 8 for Phase 1 participants and Visit 4 for Phase 2/3 participants).

For BNT162b2-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, SAEs will be collected from the time the participant provides informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group).

For BNT162b2-naïve participants in the subset for evaluation of protection against emerging VOCs, SAEs will be collected from the time the participant provides informed consent through and including Visit 405 (6 months after the second dose).

The safety endpoints "SAEs from Dose 1 to 6 months after the second dose" and "SAEs from Dose 1 to 5 or 6 months after the last dose" for evaluation of boostability and protection against emerging VOCs will be summarized by SOC and PT at the participant level. For the subset for evaluation of boostability and protection against emerging VOCs, Dose 1 refers to the first dose of BNT162b2$_{SA}$ or first dose of BNT162b2 booster.

3.1.1.6. Hematology and Chemistry Laboratory Parameters (for Phase 1 Only)

For participants in Phase 1, below are the additional primary safety endpoints:

- Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2.

The following safety laboratory tests will be performed at the times defined in the protocol, Section 1.3 (schedule of activities). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 8). Additionally, the primary criterion for abnormality will follow the Pfizer safety rule book.

Table 8. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5

Table 8. Laboratory Abnormality Grading Scale

WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm^3	2500 – 3500	1500 – 2499	1000 – 1499	<1000
Lymphocytes decrease - cells/mm^3	750 – 1000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1500 – 2000	1000 – 1499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Alkaline phosphate - increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	>10 × ULN
Liver function tests - ALT, AST increase by factor	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10 × ULN
Bilirubin - when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	>1.75 × ULN
Bilirubin - when liver function test is normal - increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	>3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

3.1.2. Immunogenicity Endpoints (for the Phase 2/3 Subset for Evaluation of Boostability and Protection Against Emerging VOCs Only)

- SARS-CoV-2 reference strain NTs.
- SARS-CoV-2 SA NTs.

In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics.

Titers (and IgG concentrations, secondary and exploratory endpoints) 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.

3.1.3. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (prior to 7 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 7 days after the second dose).

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT (counting cases from 7 days after the second dose).

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

Phase 1

In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention:

- 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.

Below are the secondary immunogenicity endpoints for Phase 1:

- SARS-CoV-2 neutralizing titers.

- S1-binding IgG levels.

- RBD-binding IgG levels.

Phase 2/3

Participants 12 to 15 years of age and 16 to 25 years of age:

- SARS-CoV-2 neutralizing titers.

Participants in the subset for evaluation of boostability and protection against emerging VOCs:

- SARS-CoV-2 reference strain NTs.

- SARS-CoV-2 SA NTs.

In order to allow direct comparability with the reference strain, the anti-SA NTs may be adjusted to account for intrinsic variant or assay characteristics.

3.2.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (prior to 14 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 14 days after the second dose).

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT (counting cases from 14 days after the second dose).

- Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (prior to 7 days and prior to 14 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 7 days and 14 days after the second dose).

- Confirmed severe COVID-19 incidence per 1000 person-years of follow-up (counting cases from 7 days and 14 days after the second dose).

- According to the CDC-defined symptoms, COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (prior to 7 days and prior to 14 days after receipt of the second dose) of past SARS-CoV-2 infection (counting cases from 7 days and 14 days after the second dose).

- According to the CDC-defined symptoms, COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT (counting cases from 7 days and 14 days after the second dose).

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19.

- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection.

3.3. Exploratory Endpoints

3.3.1. Safety Endpoints (for Phase 1 Boostability Assessment Only)

- Local reactions (pain at the injection site, redness, and swelling) for up to 7 days after Dose 3.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days after Dose 3.
- AEs from Dose 3 to 1 month after Dose 3.
- SAEs from Dose 3 to 1 month after Dose 3.

3.3.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

- COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT in participants without, and with and without, evidence of infection (counting cases from 7 days after the second dose).
- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants who received BNT162b2 at initial randomization or subsequently (counting cases from 7 days after the second BNT162b2 vaccination).
- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19.
- Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection.

3.3.3. Immunogenicity Endpoints

In Phase 1 participants participating in boostability assessment at the following time points after receipt of a third dose of BNT162b2:

- At the time of Dose 3 and 7 days and 1 month after Dose 3.

Below are the exploratory immunogenicity endpoints for Phase 1:

- SARS-CoV-2 reference-strain neutralizing titers.
- SARS-CoV-2 SA-variant neutralizing titers.
- Full-length S-binding or S1-binding IgG levels.

In Phase 2/3 participants at the following time points after receipt of study intervention:

- Baseline and 1, 6, 12, and 24 months after completion of vaccination.

Below are the exploratory immunogenicity endpoints for Phase 2/3:

- SARS-CoV-2 neutralizing titers.
- Full-length S-binding or S1-binding IgG levels.

3.3.4. Additional Endpoints (for Phase 2/3 Only)

- All safety, immunogenicity, and efficacy endpoints described above will be summarized separately for participants with confirmed stable HIV.
- AEs, SAEs, and SARS-CoV-2 neutralizing titers will be summarized separately for participants 16 to 55 of age vaccinated with study intervention produced by manufacturing "Process 1" and each lot of "Process 2." All participants who received "Process 2" vaccine and a random sample of 250 participants 16 to 55 years of age selected from those who received "Process 1" vaccine will be included for the side-by-side descriptive summary of "Process 1" and each lot of "Process 2."
- Identification of SARS-CoV-2 variant(s).
- SARS-CoV-2 NTs for any VOCs not already specified.
- Cell-mediated immune response endpoints.

3.4. Baseline and Other Variables

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

3.4.1. Demographics, Medical History, and Physical Examination

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

Age at the time of vaccination (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 19th birthday, the participant is considered to be 18 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination at 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.

For Phase 1, a physical examination will be performed. It will evaluate any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Clinically significant abnormal results will be recorded in the CRF.

For Phase 2/3, If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, physical examination will be performed and recorded any findings in the source documents and, if clinically significant, it will be recorded on the medical history CRF.

3.4.2. E-Diary Completion

For all participants in Phase 1, a subset of at least 6000 in Phase 2/3, and participants in the subset for evaluation of boostability and protection against emerging VOCs, an e-diary will be considered transmitted if any data for local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

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

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants). In addition, for Phase 1 participants who go on to receive a third dose of BNT162, concomitant vaccinations will be collected from the time the participant provides informed consent (for receipt of Vaccination 3) through and including Visit 8c (1 month after the third dose). For BNT162-experienced participants in the subset for evaluation of boostability and protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to the time the participant provides informed consent (for participation in the subset) through and including Visit 306. For BNT162b2-naïve participants in the subset for evaluation of protection against emerging VOCs, all vaccinations received will be recorded from 28 days prior to study enrollment through and including Visit 405.

- Prohibited medications listed in the protocol, Section 6.5.1, will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.

- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

3.5. Safety Endpoints

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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 classifications will be documented per SOPs.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result from the blood collection within an appropriate window after Dose 1 (same as visit window, ie, within 19-23 days after Dose 1), and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood collection 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.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive a third dose of BNT162b2 or $BNT162b2_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.
Dose 4 booster evaluable immunogenicity	All eligible randomized participants who receive 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window, receive 2 booster doses of $BNT162b2_{SA}$ as rerandomized, have at least 1 valid and determinate immunogenicity result after Dose 4 from a blood collection within an appropriate window, and have no other important protocol deviations as determined by the clinician.

Population	Description
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Dose 3 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive a third dose of BNT162b2 or $BNT162b2_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 3.
Dose 4 booster all-available immunogenicity	All randomized participants who receive 2 doses of BNT162b2 at initial randomization, receive 2 booster doses of $BNT162b2_{SA}$ at rerandomization, and have at least 1 valid and determinate immunogenicity result after Dose 4.
Evaluable efficacy (7 days)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
Evaluable efficacy (14 days)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 14 days after Dose 2.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to Dose 2.
Evaluable efficacy (asymptomatic surveillance)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), consented to participate in the asymptomatic surveillance, and have no other important protocol deviations as determined by the clinician on or before the start of the asymptomatic surveillance period.
All-available efficacy	Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination. Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses.

Population	Description
Safety	All randomized participants who receive at least 1 dose of the study intervention. Analyses of reactogenicity endpoints will be based on a subset of the safety population that includes participants with any e-diary data reported after vaccination.

The important protocol deviations will be determined by the medical monitor. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity/efficacy, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis in Phase 2/3 is carried out.

5. GENERAL METHODOLOGY AND CONVENTIONS

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 6.3. The timing for statistical analyses is specified in Section 7.

5.1. Hypotheses and Decision Rules

5.1.1. Vaccine Efficacy Hypothesis

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as VE = 100 × (1 – IRR). IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the active vaccine group to the corresponding illness rate in the placebo group (see Appendix 3 for details on the calculation of IRR and VE). The assessment of VE will be based on posterior probabilities of VE_1 >30% and VE_2 >30% using beta-binomial models. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (high posterior probability) that either VE_1 >30% or both VE_1 and VE_2 are >30%. The assessment for the primary analysis will be based on posterior probability using a beta-binomial model (see Appendix 2 for details).

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) will be evaluated based on the lower bound of the 95% CI calculated using the Clopper-Pearson method. VE will be demonstrated if the lower bound of the 2-sided 95% CI for VE is >20%.

5.1.2. Immunogenicity Hypothesis

5.1.2.1. Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

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

where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

5.1.2.2. Hypothesis for Boostability and Protection Against Emerging SARS-CoV-2 VOCs

The primary and secondary objectives for boostability and protection against emerging VOCs for BNT162b2-experienced participants and BNT162b2-naïve participants will be assessed based on:

- GMRs of SARS-CoV-2 SA and/or reference strain neutralizing titers using a 2-fold noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the GMR is >0.5.

- The difference in percentages of participants with seroresponse to the SA strain and/or the reference strain using a 10% noninferiority margin. Noninferiority is met if the lower limit of the alpha-adjusted CI for the difference in percentages of participants with seroresponse is >-10%.

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

5.1.3. Sample Size

5.1.3.1. Phase 1

Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

5.1.3.2. Efficacy Against COVID-19

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of study intervention, a total of approximately 164 first confirmed COVID-19 illness cases will provide approximately 90% power. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

5.1.3.3. Efficacy Against Asymptomatic Infection

The secondary objectives regarding VE against asymptomatic SARS-CoV-2 infection will be assessed in Phase 2/3 participants (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT). Assuming a true VE of 70%, a total of 53 asymptomatic cases will provide approximately 90% power to conclude true VE>20%. A total of 206 cases is needed to have 90% power if the true VE is 50%. The hypothesis for asymptomatic seroconversion of N-binding antibody will be tested if at least 206 cases are accrued. The hypothesis for asymptomatic infection based on central laboratory–confirmed NAAT in participants who are consented to participate in the intensive surveillance phase will be tested if at least 53 cases are accrued.

5.1.3.4. Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 280 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group will provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 9).

Table 9. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviation: GMR = geometric mean ratio; GMT = geometric mean titer.
a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).
b. At 0.05 alpha level (2-sided).

5.1.3.5. Boostability and Protection Against Emerging SARS-CoV-2 VOCs

To assess boostability and protection against emerging SARS-CoV-2 VOCs, approximately 300 participants will be enrolled in each of the 3 groups (BNT162b2-experienced participants to receive either a third dose of BNT162b2 [Group 1] or a third dose of BNT162b2$_{SA}$ [Group 2], BNT162b2-naïve participants to receive 2 doses of BNT162b2$_{SA}$ [Group 3]) to provide an acceptable safety database.

Assuming a 20% nonevaluable rate, approximately 240 evaluable participants in each group will contribute to immunogenicity evaluation. This will provide sufficient power for noninferiority evaluations with appropriate multiplicity adjustment for type I error control.

For comparisons based on GMR, the assay standard deviation in log scale is assumed to be 0.74 based on results from Phase 2 of the study and adjusted for assay variability. A GMR of 1 is assumed for each comparison.

For comparisons based on seroresponse, a 90% response rate is assumed for each comparative group or at each comparative time point.

Within-Group Comparison for BNT162b2-Experienced Participants

For each randomized group of BNT162b2-experienced participants (Group 1: received a third dose of BNT162b2, and Group 2: received a third dose of BNT162b2$_{SA}$), with 240 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has >99.9% power to demonstrate noninferiority based on GMR for the objectives in vaccine-experienced individuals using a 2-fold margin.

Assuming a true response rate of 90% in each group, the study has 89.7% power to show noninferiority based on seroresponse rate for the objectives in vaccine-experienced individuals using a 10% margin.

Between-Group Comparison of BNT162b2-Naïve Participants to Selected Existing Phase 3 Participants Who Received 2 Doses of BNT162b2

Approximately 300 participants will be selected from the existing Phase 3 participants who received 2 doses of BNT162b2 to form the control group for the BNT162b2-naïve participants. The selection will ensure comparable distribution of age, sex, and other demographic factors in the control group and BNT162b2-naïve group. With 240 evaluable BNT162b2-naïve participants and 240 evaluable participants in the control group and the above-stated assumptions for the GMR, standard deviation, and seroresponse rate, the study has >99.9% power to declare noninferiority based on GMR for the objectives in vaccine-naïve individuals using a 2-fold margin and 89.7% power to declare noninferiority based on seroresponse rate using a 10% margin.

5.1.3.6. Safety

For safety outcomes, Table 10 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

Table 10. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=300	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.03	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.06	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.11	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.16	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.21	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.26	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.36	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.45	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.53	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.59	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.65	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.78	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	0.95	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

5.1.4. Multiplicity Considerations

5.1.4.1. Phase 1

For Phase 1, there is no hypothesis testing.

5.1.4.2. Phase 2/3 Vaccine Efficacy

For Phase 2/3, a Bayesian approach will be applied for the first primary efficacy endpoint at the interim and final analyses. The boundaries for declaring efficacy at interim analyses and success criteria for the final analysis are adjusted appropriately to control the type I error at 0.025 (Table 13).

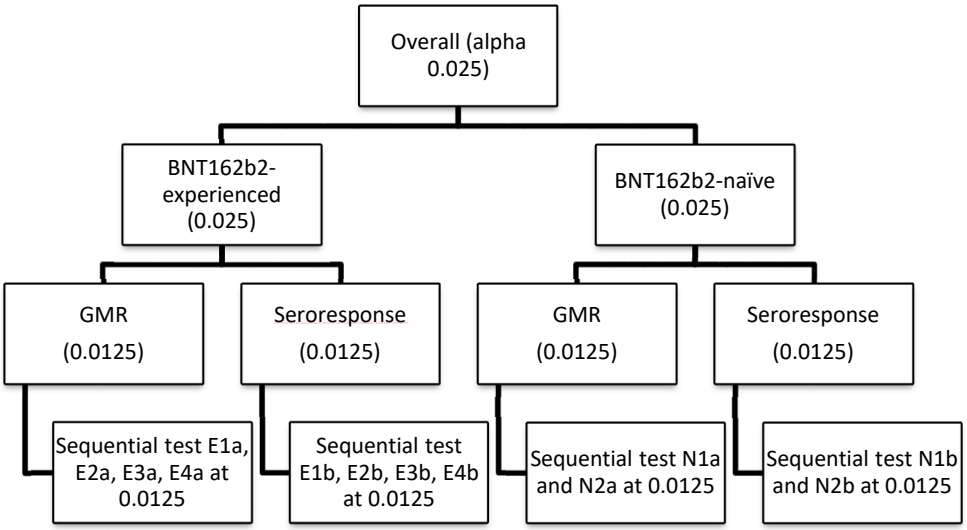
5.1.4.3. Phase 2/3 Immunogenicity

Figure 1 outlines the type I error control strategy for multiple objectives across different populations (BNT162b2-experienced or BNT162b2-naïve) and estimands (GMR or seroresponse).

The objectives for BNT162b2-experienced participants and BNT162b2-naïve participants will be evaluated independently. The vaccine-experienced and vaccine-naïve individuals are different populations with different objectives. The 2 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments will be applied to the assessments of the 2 populations.

For each population, the objectives will be evaluated separately for each estimand. To control the overall type I error, the 1-sided alpha of 0.025 will be split and allocated equally to each estimand. Specifically, for each estimand, the hypotheses will be tested in sequential order (as listed in the objectives in Section 3) using a 1-sided alpha of 0.0125 (Figure 1, where E and N represent vaccine-experienced and vaccine-naïve, respectively, and a and b represent GMR and seroresponse estimands, respectively).

Figure 1. Multiplicity Schema



5.2. General Methods

Time points for local reactions and systemic events refer to data within 7 days after each dose. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

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 method.[2]

For Phase 2/3 only, the 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen[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.

A Bayesian beta-binomial model with a minimally informative prior will be also used for VE primary endpoints (see Appendix 2).

5.2.2. Analyses for Count Data

The number of occurrences of a certain event is count data and thus could be modeled using Poisson distribution. The incidence rate is estimated as the number of events observed divided by the total person-years of follow-up.

Assuming an observed event is from Poisson distribution with parameter λT, where λ is the incidence rate and T is the total person-years of follow-up, based on the relationship between the Poisson and chi-square distribution,[3] the exact lower and upper α-percent 2-sided confidence limits for λT can be estimated by:

$Y_l = \frac{\chi^2_{2Y,\alpha/2}}{2}$ and $Y_u = \frac{\chi^2_{2(Y+1),1-\alpha/2}}{2}$, respectively, where Y is the number of events observed.

The exact lower and upper confidence limit for incidence rate λ can then be obtained as Y_l/T and Y_u/T, respectively.

5.2.3. Analyses for Continuous Data

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

5.2.3.1. Geometric Means

For immunogenicity results of SARS-CoV-2 neutralizing titers, the GMTs will be computed along with associated 95% CIs. The GMTs 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 titers, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits. Similarly, GMCs and 95% CIs will be calculated for S1-binding IgG levels and RBD-binding IgG levels.

5.2.3.2. Geometric Mean Fold Rises

GMFRs will be defined as the result after vaccination divided by the result 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 neutralization titers or antibody levels (later result minus earlier result) and exponentiating the mean. The associated 2-sided 95% CIs are obtained by constructing CIs using Student's t-distribution for the mean difference on the natural log scale and exponentiating the confidence limits.

5.2.3.3. Geometric Mean Ratios

For SARS-CoV-2 neutralizing titers and S1-binding IgG levels and RBD-binding IgG levels, the GMRs will be provided along with associated 95% CIs. GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG levels/RBD-binding IgG levels at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) 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.

For SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age and 16 to 25 years of age, the GMRs will be provided along with associated 95% CI. The GMR and its 2-sided 95% CI 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 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

For assessment of boostability and protection against emerging VOCs, the comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 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.

For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean. The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits.

5.2.3.4. Geometric Mean Fold Rise Ratios

The ratios of GMFR A to GMFR B and GMFR A to GMFR C may be explored, where GMFR A is the GM of the ratio of the SARS-CoV-2 neutralizing titer at the time point after vaccination to the corresponding titer at the time point before vaccination, GMFR B is the GM of the ratio of the S1-binding IgG level at the time point after vaccination to the corresponding antibody level at the time point before vaccination, and GMFR C is the GM of the ratio of the RBD-binding IgG level at the time point after vaccination to the corresponding antibody level at the time point before vaccination.

5.2.3.5. 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

For endpoints, the missing data handling rules are described in the corresponding endpoint sections.

For the missing dates, the sponsor data standard rules for imputation will be applied (eg, partial dates for AEs will be imputed according to Pfizer standard algorithms).

Missing COVID-19 test data in Phase 2/3 for computing VE will be imputed in the sensitivity analysis. Details are included in Section 6.1.3.1.2.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Safety Endpoints

The safety analyses are based on the safety population. Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after vaccination. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each and any local reaction after each dose in each vaccine group 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. Supplementary 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, analysis methodology, and appropriate 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.

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days will be plotted for each vaccine 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

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each dose (Section 2.1).

- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination; missing values will not be imputed.
- Reporting results: Descriptive statistics for each systemic event after each dose in each vaccine group 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. Supplementary 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.

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.

Figures:

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

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 1 to 1 month after the second dose for all phases, from Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2, and from Dose 1 (of booster BNT162b2 or BNT162b2$_{SA}$) to 1 month after the last dose for participants in the Phase 3 subset for evaluation of boostability and protection against emerging VOCs (Section 2.1).
- Analysis set: Safety population (Section 4).

- Analysis time point: Dose 1 to 1 month after the second dose for all phases, Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2, Dose 1 (of booster BNT162b2 or BNT162b2$_{SA}$) to 1 month after the last dose for participants in the Phase 3 subset for evaluation of boostability and protection against emerging VOCs.

- Analysis methodology: Descriptive statistics (Section 5.2.1) for all phases and additional 3-tiered approach for Phase 2/3 (Section 3.1.1.4).

- Intercurrent events and missing data: Partial AE dates will be imputed using the Pfizer standard algorithm.

- Reporting results: AEs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs for Phase 2/3 only. Under this approach AEs are classified into 1 of 3 tiers (Section 3.1.1.4). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the active vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[2] method will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within SOC. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs for each vaccine group.

6.1.1.3.2. Supplementary Analyses

Immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine 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 to 6 months after the second dose for all phases, from Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2, and from Dose 1 (of booster BNT162b2 or BNT162b2$_{SA}$) to 5 or 6 months after the last dose for participants in the Phase 3 subset for evaluation of boostability and protection against emerging VOCs (Section 2.1).

- Analysis set: Safety population (Section 4).

- Analysis time point: Dose 1 to 6 months after the second dose for all phases, Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2, Dose 1 (of booster BNT162b2 or BNT162b2$_{SA}$) to 5 or 6 months after the last dose for participants in the Phase 3 subset for evaluation of boostability and protection against emerging VOCs.

- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Partial SAE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs will be provided for each vaccine group.

6.1.1.5. Hematology and Chemistry Parameters (for Phase 1 Only)

6.1.1.5.1. Main Analyses

- Estimands: The percentage of participants with abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 (Section 2.1).
- The percentage of participants with grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: 1 and 7 days after Dose 1; and 7 days after Dose 2.
- Analysis methodology: Descriptive statistics including counts and percentage (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive summary statistics will be provided including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.

6.1.2. Immunogenicity Endpoints (for the Phase 2/3 Subset for Evaluation of Boostability and Protection Against Emerging VOCs Only)

6.1.2.1. SARS-CoV-2 Reference Strain NT and SA NT at 1 Month After Dose 3 vs Reference Strain NT at 1 Month After Dose 2 in BNT162b2-Experienced Participants

6.1.2.1.1. Main Analyses

- Estimands:
  - E1a: GMR of reference strain NT 1 month after the third dose of BNT162b2 to 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).
  - E2a: GMR of SA NT 1 month after 1 dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).

- Analysis set: Dose 3 booster evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after the second dose of BNT162b2, 1 month after the third dose of BNT162b2, and 1 month after 1 dose of BNT162b2$_{SA}$.

- Analysis methodology: The comparisons of different NTs (anti-SA or anti–reference strain) or the same NTs at different time points within the same group will be limited to participants with nonmissing values at both time points or both NT measurements. GMRs will be calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, later time point minus earlier time point) and exponentiating the mean (Section 5.2.3.3). The associated 2-sided 97.5% 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. Noninferiority of E1a and E2a will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5.

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 97.5% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 SA and reference strain NTs at each time point.

6.1.2.2. Seroresponse to the Reference Strain and SA Strain at 1 Month After Dose 3 vs Seroresponse to the Reference Strain at 1 Month After Dose 2 in BNT162b2-Experienced Participants

6.1.2.2.1. Main Analyses

- Estimands:

  - E1b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after the third dose of BNT162b2 and 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).

  - E2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).

- Analysis set: Dose 3 booster evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after the second dose of BNT162b2, 1 month after the third dose of BNT162b2, and 1 month after 1 dose of BNT162b2$_{SA}$.

- Analysis methodology: The percentages of participants with seroresponse at each time point and the difference in percentages will be provided. The 2-sided 97.5% CIs for the difference in percentages of participants with seroresponse will be calculated using the Miettinen and Nurminen method (Section 5.2.1). Noninferiority of E1b and E2b will be assessed sequentially. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 97.5% CIs will be provided.

6.1.2.3. SARS-CoV-2 SA NT at 1 Month After Dose 2 vs Reference Strain NT at 1 Month After Dose 2 in BNT162b2-Naïve Participants

6.1.2.3.1. Main Analyses

- Estimands:

  - N1a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 (Section 2.1).

- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after the second dose of BNT162b2 and 1 month after the second dose of BNT162b2$_{SA}$.

- Analysis methodology: For the between-group comparison, GMRs will be calculated as the mean of the difference of logarithmically transformed assay results between 2 groups and exponentiating the mean (Section 5.2.3.3). The associated 2-sided 97.5% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed titers and exponentiating the confidence limits. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5.

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 97.5% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 SA and reference strain NTs at each time point for each vaccine group.

6.1.2.4. Seroresponse to the SA Strain at 1 Month After Dose 2 vs Seroresponse to the Reference Strain at 1 Month After Dose 2 in BNT162b2-Naïve Participants

6.1.2.4.1. Main Analyses

- Estimands:
  - N1b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 (Section 2.1).
- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after the second dose of BNT162b2 and 1 month after the second dose of BNT162b2$_{SA}$.
- Analysis methodology: The difference in percentages of participants with seroresponse and associated 2-sided 97.5% CIs will be calculated in the same way as for primary endpoints E1b and E2b. Noninferiority will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than -10%.
- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.
- Reporting results: The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 97.5% CIs will be provided.

6.1.3. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

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

6.1.3.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

- 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy (7 days) and all-available efficacy populations (Section 4).

- Analysis time point: At interim analyses and final analysis when the surveillance period ends.

- Analysis methodology: Assessment of VE will be performed for confirmed COVID-19 from 7 days after the receipt of the second dose of study intervention onwards, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of COVID-19 illness rate per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group after the second dose (see Appendix 3 for details on the derivation of IRR and VE). The posterior probability (ie, P[VE >30%|data]) at each interim analysis and final analysis will be computed using a beta-binomial model and a specified minimally informative beta distribution as prior (details can be found in Appendix 2).

- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed in the main analyses.

- Reporting results: The point estimate of VE, 95% credible intervals using the 2.5th percentile and the 97.5th percentile, and Bayesian posterior probability of VE greater than 30% will be provided (details can be found in Appendix 2).

6.1.3.1.2. Sensitivity and Supplemental Analyses

With MAR assumption, a missing efficacy endpoint (laboratory-confirmed COVID-19 results) may be imputed based on predicted probability using the fully conditional specification method.[4] The imputation will run multiple times (up to 1000) and summary statistics similar to those used in the main analysis will be tabulated across the imputations. Other imputation methods without the MAR assumption may be explored, eg, a tipping point analysis.

All COVID-19 cases after Dose 1 may be analyzed using the Dose 1 all-available efficacy population. COVID-19 disease-related information may be summarized or listed.

After the final efficacy analyses at 164 first primary cases, updated efficacy analyses will be performed with additional data accrued. The point estimate of VE in the blinded follow-up period and associated 2-sided 95% CI will be derived using the Clopper Pearson method adjusted for surveillance time, and the posterior probability (ie, P[VE >30%|data]) will be provided. VE at different follow-up time intervals and against different variant strains may be assessed.

Efficacy could also be assessed over a longer time period using time-to-event data analysis methods to account for censoring (participants censored when they receive other vaccines or withdraw) as well as potentially confounding factors. A Kaplan-Meier curve showing the cumulative incidence of COVID-19 cases over time may also be informative to understand the sustainability of VE.

For the assessment of efficacy in the presence of potential crossover, the established adjusting methods may be considered. For example, a rank-preserving structural failure time model may be appropriate to attempt to reconstruct data for the control arm as if crossover had not occurred, with the aim of reducing bias and allowing the vaccine effect to be assessed more accurately.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

Phase 1

The statistical analysis of immunogenicity results for Phase 1 will be primarily based on the Dose 1 and Dose 2 evaluable immunogenicity populations. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations. An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

Phase 2/3

The statistical analysis of immunogenicity results for Phase 2/3 will be based on Dose 2 evaluable immunogenicity population. Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity population. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

6.2.1.1. SARS-CoV-2 Neutralizing Titers (Phase 1)

6.2.1.1.1. Main Analyses

- Estimands:
  - GMTs (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).

- Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination (Section 2.1).

- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results (Section 5.2.3.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiated to transform results back to the original scale. 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 (Section 5.2.3.2). Percentages of participants with ≥4-fold rise will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: the GMTs at each time point, GMFRs from before vaccination to each subsequent time point after vaccination, and the percentages of participants achieving ≥4-fold rise and the associated 2-sided 95% CIs from before vaccination to each time point after vaccination.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers after Dose 1 and after Dose 2 (Section 5.2.3.5).

6.2.1.2. S1-Binding IgG Levels and RBD-Binding IgG Levels (Phase 1)

6.2.1.2.1. Main Analyses

- Estimands:

  - GMCs (Section 2.1).

  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).

  - Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination (Section 2.1).

- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results (Section 5.2.3.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later time point – earlier time point). 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 (Section 5.2.3.2). Percentages of participants with ≥4-fold rise will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).

- Intercurrent events and missing data: Concentrations below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: the GMCs, GMFRs, and percentages of participants with ≥4-fold rise and the associated 2-sided 95% CIs will be provided for each study intervention (active/placebo) within each group before vaccination and at each time point.

Figures:

Empirical RCDCs will be provided for S1-binding IgG levels and RBD-binding IgG levels after Dose 1 and after Dose 2 (Section 5.2.3.5).

6.2.1.3. SARS-CoV-2 Neutralizing Titers vs SARS-CoV-2 S1-Binding IgG Levels and RBD-Binding IgG Levels (Phase 1)

6.2.1.3.1. Main Analyses

- Estimands:
  - GMR of SARS-CoV-2 neutralizing titers to S1-binding IgG levels (Section 2.1).
  - GMR of SARS-CoV-2 neutralizing titers to RBD-binding IgG levels (Section 2.1).

- Analysis set: Dose 1 and Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2.

- Analysis methodology: GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level or RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG levels for each participant) and exponentiating the mean (Section 5.2.3.3). 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 (Section 5.2.3.3).

- Intercurrent events and missing data: Concentrations below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMRs and the associated 2-sided 95% CIs will be provided for each study intervention within each group before vaccination and at each time point.

6.2.1.4. SARS-CoV-2 Neutralizing Titers in Participants 12 to 15 Years of Age vs Those 16 to 25 Years of Age (Phase 2/3)

6.2.1.4.1. Main Analyses

- Estimands: GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination (Section 2.1).

- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after Dose 2.

- Analysis methodology: The GMR and its 2-sided 95% CI 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 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 (Section 5.2.3.3).

- Intercurrent events and missing data: Concentrations below the LLOQ or 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. Missing data will not be imputed.

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

6.2.1.4.2. Supplemental Analyses

The counts, percentages of participants with seroresponse (achieving ≥4-fold rise from baseline, as defined in Section 5.1.2.2), the difference in percentages between the 2 age groups (12-15 years of age minus 16-25 years of age), and the associated 2-sided 95% CIs will be provided.

6.2.1.5. SARS-CoV-2 SA NT and Reference Strain NT at 1 Month After Dose 3 vs Reference Strain NT at 1 Month After Dose 2 in BNT162b2-Experienced Participants

6.2.1.5.1. Main Analyses

- Estimands:
  - E3a: GMR of SA NT 1 month after the third dose of BNT162b2 to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).
  - E4a: GMR of reference strain NT 1 month after 1 dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).
- Analysis set: Dose 3 booster evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after the second dose of BNT162b2, 1 month after the third dose of BNT162b2, and 1 month after 1 dose of BNT162b2$_{SA}$.
- Analysis methodology: GMRs and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1a and E2a (Section 6.1.2.1.1). If noninferiority is established for both E1a and E2a, E3a and E4a will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.5).
- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.
- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 97.5% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 SA and reference strain NTs at each time point.

6.2.1.6. Seroresponse to the SA Strain and Reference Strain at 1 Month After Dose 3 vs Seroresponse to the Reference Strain at 1 Month After Dose 2 in BNT162b2-Experienced Participants

6.2.1.6.1. Main Analyses

- Estimands:
  - E3b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the third dose of BNT162b2 and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).
  - E4b: The difference in percentages of participants with seroresponse to the reference strain at 1 month after 1 dose of $BNT162b2_{SA}$ and 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).
- Analysis set: Dose 3 booster evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after the second dose of BNT162b2, 1 month after the third dose of BNT162b2, and 1 month after 1 dose of $BNT162b2_{SA}$.
- Analysis methodology: The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b (Section 6.1.2.2.1). If noninferiority is established for both E1b and E2b, E3b and E4b will be assessed sequentially using the same criterion (lower bound of the 2-sided 97.5% CI for the difference in percentages is greater than -10%).
- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.
- Reporting results: The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 97.5% CIs will be provided.

6.2.1.7. SARS-CoV-2 SA NT After Dose 3 (BNT162b2-Experienced Participants)

6.2.1.7.1. Main Analyses

- Estimands:
  - GMR of SA NT 1 month after 1 dose of $BNT162b2_{SA}$ to 1 month after the third dose of BNT162b2 (Section 2.1).
  - The difference in percentages of participants with seroresponse to the SA strain at 1 month after 1 dose of $BNT162b2_{SA}$ and 1 month after the third dose of BNT162b2 (Section 2.1).

- Analysis set: Dose 3 booster evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after the third dose of BNT162b2 and 1 month after 1 dose of BNT162b2$_{SA}$.

- Analysis methodology: GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a (Section 6.1.2.3.1). The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b (Section 6.1.2.4.1).

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 95% CIs will be provided. The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 95% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 SA NTs at each time point for each vaccine group.

6.2.1.8. SARS-CoV-2 SA NT at 1 Month After Dose 4 vs Reference Strain NT at 1 Month After Dose 2 in BNT162b2-Experienced Participants

6.2.1.8.1. Main Analyses

- Estimands:

  - GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to the reference strain NT 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).

  - The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and seroresponse to the reference strain at 1 month after the second dose of BNT162b2 in the same individuals (Section 2.1).

- Analysis set: Dose 4 booster evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after the second dose of BNT162b2 and 1 month after the second dose of BNT162b2$_{SA}$.

- Analysis methodology: GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoints E1a and E2a (Section 6.1.2.1). The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints E1b and E2b (Section 6.1.2.2.1).

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 95% CIs will be provided. The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 95% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 SA and reference strain NTs at each time point.

6.2.1.9. SARS-CoV-2 SA NT at 1 Month After Dose 2 (BNT162b2-Naïve Participants)

6.2.1.9.1. Main Analyses

- Estimands:

  - N2a: GMR of SA NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 (Section 2.1).

- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1 month after the second dose of BNT162b2 and 1 month after the second dose of BNT162b2$_{SA}$.

- Analysis methodology: GMR and the associated 2-sided 97.5% CI will be calculated in the same way as for the primary endpoint N1a (Section 6.1.2.3.1). Statistical superiority of N2a will be assessed if noninferiority of N1a is established. Superiority of N2a will be declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 1.

- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 97.5% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 SA at each time point for each vaccine group.

6.2.1.10. Seroresponse to the SA Strain at 1 Month After Dose 2 (BNT162b2-Naïve Participants)

6.2.1.10.1. Main Analyses

- Estimands:
  - N2b: The difference in percentages of participants with seroresponse to the SA strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 (Section 2.1).
- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after the second dose of BNT162b2 and 1 month after the second dose of BNT162b2$_{SA}$.
- Analysis methodology: The difference in percentages of participants with seroresponse and the associated 2-sided 97.5% CIs will be calculated in the same way as for the primary endpoints E1b and E2b (Section 6.1.2.2.1). Statistical superiority of N2b will be assessed if noninferiority of N1b is established. Superiority of N2b will be declared if the lower bound of the 2-sided 97.5% CI for the difference in percentages of participants with seroresponse is greater than 0%.
- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.
- Reporting results: The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 97.5% CIs will be provided.

6.2.1.11. Reference Strain NT at 1 Month After Dose 2 (BNT162b2-Naïve Participants)

6.2.1.11.1. Main Analyses

- Estimands:
  - GMR of reference strain NT 1 month after the second dose of BNT162b2$_{SA}$ to 1 month after the second dose of BNT162b2 (Section 2.1).
  - The difference in percentages of participants with seroresponse to the reference strain at 1 month after the second dose of BNT162b2$_{SA}$ and 1 month after the second dose of BNT162b2 (Section 2.1).

- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).
- Analysis time points: 1 month after the second dose of BNT162b2 and 1 month after the second dose of BNT162b2$_{SA}$.
- Analysis methodology: GMR and the associated 2-sided 95% CI will be calculated in the same way as for the primary endpoint N1a (Section 6.1.2.3.1). The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs will be calculated in the same way as for the primary endpoints N1b (Section 6.1.2.4.1).
- Intercurrent events and missing data: Titers below the LLOQ or 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. Missing data will not be imputed.
- Reporting results: The GMTs at each time point, GMRs, and the associated 2-sided 95% CIs will be provided. The counts, percentages of participants with seroresponse at each time point, the difference in percentages, and the associated 2-sided 95% CIs will be provided.

Figures:

Empirical RCDCs will be provided for SARS-CoV-2 reference strain NTs at each time point for each vaccine group.

6.2.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

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

6.2.2.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (14 days) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period or at IAs if requested.
- Analysis methodology: the same method used for primary VE endpoints will be applied (Section 6.1.3.1.1).

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: the same output generated for primary VE endpoints will be provided (Section 6.1.3.1.1).

6.2.2.2. Confirmed Severe COVID-19 Incidence per 1000 Person-Years of Follow-up

6.2.2.2.1. Main Analyses

- Estimands:

  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].

- Analysis set: Evaluable efficacy (7 days and 14 days) and all-available efficacy populations (Section 4).

- Analysis time point: End of the surveillance period or at IAs if requested.

- Analysis methodology: the same method used for primary VE endpoints will be applied (Section 6.1.3.1.1).

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: the same output generated for primary VE endpoints will be provided (Section 6.1.3.1.1).

6.2.2.2.2. Supplemental Analyses

All severe COVID-19 cases occurring after Dose 1 will be summarized descriptively.

After the final efficacy analyses at 164 first primary cases, updated efficacy analyses will be performed for severe COVID-19 incidence from 7 days after the second dose with additional data accrued. The point estimate of VE in the blinded follow-up period and associated 2-sided 95% CI will be derived using the Clopper Pearson method adjusted for surveillance time, and the posterior probability (ie, P[VE >30%|data]) will be provided.

In addition to the protocol definition of severe COVID-19, supportive analyses using the CDC definition of severe COVID-19 will be performed.

6.2.2.3. Confirmed COVID-19 Incidence per 1000 Person-Years of Follow-up (According to the CDC-Defined Symptoms)

6.2.2.3.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days and 14 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (7 days and 14 days) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: Assessment of VE will be performed for centrally confirmed COVID-19 according to the CDC-defined symptoms from 7 days and from 14 days after the receipt of the second dose of study intervention onwards, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of COVID-19 illness rate according to the CDC-defined symptoms per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.2.2.4. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the N-Binding Antibody Seroconversion)

6.2.2.4.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19 for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (seroconversion) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period.
- Analysis methodology: An asymptomatic case (Appendix 4) is defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT at Visit 1 and Visit 2 and at the time of a potential COVID-19 illness). A secondary definition will be applied without the requirement for a negative NAAT at Visit 2. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time. The VE is demonstrated if the lower bound of the 2-sided 95% CI for VE is greater than 20%. The analysis of the primary definition of asymptomatic cases will be based on the evaluable efficacy (seroconversion) population and the Dose 2 all-available efficacy population. The analysis of the secondary definition of asymptomatic cases will be based on the Dose 1 all-available efficacy population.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.2.2.4.2. Supplemental Analyses

Descriptive summary of VE against asymptomatic infection over different time intervals (ie, prior to 1 month after Dose 2, from 1 month after Dose 2 onward), along with the associated 2-sided 95% CI, will be calculated using the same method as above.

6.2.2.5. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the Central Laboratory–Confirmed NAAT)

6.2.2.5.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants without serological or virological evidence of infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (asymptomatic surveillance) and all-available efficacy populations (Section 4) and only participants who consented to participate in the asymptomatic surveillance.
- Analysis time point: End of the surveillance period.
- Analysis methodology: An asymptomatic case definition based on central laboratory–confirmed NAAT can be found in Appendix 5. VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time. The success criterion is met if lower bound of the 2-sided 95% CI for VE is greater than 20%.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.3. Exploratory Endpoints

6.3.1. Safety Endpoints (for Phase 1 Boostability Assessment Only)

6.3.1.1. Local Reactions

6.3.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after Dose 3 (Section 2.1).
- Analysis set: Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.
- Analysis time point: Within 7 days after Dose 3.
- Analysis methodology: Descriptive statistics (Section 5.2.1).

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

- Reporting results: Descriptive statistics for each and any local reaction after Dose 3 by initial vaccine and 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.

6.3.1.1.2. Supplementary 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, analysis methodology, and appropriate 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 initial vaccine and age group.

Figures:

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

6.3.1.2. Systemic Events

6.3.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after Dose 3 (Section 2.1).

- Analysis set: Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.

- Analysis time point: Within 7 days after Dose 3.

- Analysis methodology: Descriptive statistics (Section 5.2.1).

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

- Reporting results: Descriptive statistics for each systemic event after Dose 3 in each initial vaccine and 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.

6.3.1.2.2. Supplementary 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 initial vaccine and 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.

Figures:

Bar charts with the proportions of participants reporting each systemic event throughout 7 days after Dose 3 will be plotted for each initial vaccine and age group. The bars will be divided into severity categories to highlight the proportions of participants by severity.

6.3.1.3. Adverse Events

6.3.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from Dose 3 to 1 month after Dose 3 (Section 2.1).
- Analysis set: Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.
- Analysis time point: Dose 3 to 1 month after Dose 3.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Partial AE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: AEs will be categorized according to MedDRA terms. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs for each initial vaccine and age group.

6.3.1.3.2. Supplementary Analyses

Immediate AEs (within the first 30 minutes after Dose 3) will also be summarized for each initial vaccine and age group.

6.3.1.4. Serious Adverse Events

6.3.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from Dose 3 to 1 month after Dose 3 (Section 2.1).
- Analysis set: Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.
- Analysis time point: Dose 3 to 1 month after Dose 3.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Partial SAE dates will be imputed using the Pfizer standard algorithm.
- Reporting results: SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 3 to 1 month after Dose 3 will be provided for each initial vaccine and age group.

6.3.2. Vaccine Efficacy Endpoints (for Phase 2/3 Only)

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

6.3.2.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness based on central laboratory or locally confirmed NAAT from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness based on central laboratory or locally confirmed NAAT from 7 days after the second dose through the blinded follow-up period per 1000 person-years of follow-up in participants with and without evidence of infection for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (7 days) and all-available efficacy populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).

- Analysis methodology: After the primary objectives are met at the final analysis of at least 164 first primary cases, the study will continue with blinded follow-up until the participant is unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. A descriptive update of VE will be provided with additional follow-up data. VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness from 7 days after the second dose through the blinded follow-up period. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time.

6.3.2.1.2. Supportive Analyses

Supportive analysis of time to confirmed COVID-19 illness will be performed using Kaplan-Meier cumulative incidence curves. Participants who were randomized to placebo will be censored at the time of receipt of BNT162b2. An RPSFT model may be explored to reconstruct data for the control arm.

VE at different follow-up time intervals and against different variant strains may be assessed.

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

6.3.2.2.1. Main Analyses

- Estimands:

  - COVID-19 incidence based on central laboratory or locally confirmed NAAT from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second BNT162b2 vaccination) who received BNT162b2 at initial randomization or subsequently (Section 2.1).

  - COVID-19 incidence based on central laboratory or locally confirmed NAAT from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection who received BNT162b2 at initial randomization or subsequently (Section 2.1).

- Analysis set: Evaluable efficacy (7 days) and all-available efficacy populations (Section 4). For participants who were randomized to placebo and subsequently received BNT162b2 after being eligible according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4, the time of receipt of BNT162b2 will be reconsidered as baseline. All rules for determining evaluable efficacy and all-available efficacy populations will be similarly applied.

- Analysis time point: End of the surveillance period.

- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and exact 2-sided 95% CI based on Poisson distribution (Section 5.2.2) for confirmed COVID-19 illness from 7 days after the second BNT162b2 vaccination will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: Incidence rate and the associated 2-sided 95% CIs, and Kaplan-Meier cumulative incidence curve will be provided.

6.3.2.3. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the N-Binding Antibody Seroconversion)

6.3.2.3.1. Main Analyses

- Estimands:

    - Incidence of asymptomatic SARS-CoV-2 infection through the entire study of follow-up period per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants who received BNT162b2 and who have no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19.

- Analysis set: Evaluable efficacy and all-available efficacy populations (Section 4).

- Analysis time point: End of the surveillance period.

- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and exact 2-sided 95% CI based on Poisson distribution (Section 5.2.2) for asymptomatic infection will be provided for participants who received BNT162b2.

- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.

- Reporting results: Incidence rate and the associated 2-sided 95% CIs will be provided.

6.3.2.4. Incidence of Asymptomatic SARS-CoV-2 Infection per 1000 Person-Years of Follow-up (According to the Central Laboratory–Confirmed NAAT)

6.3.2.4.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence of past infection (up to the start of the asymptomatic surveillance period) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy (asymptomatic surveillance) and all-available efficacy populations (Section 4) and only participants who are consented to participate in the asymptomatic surveillance.
- Analysis time point: End of the surveillance period.
- Analysis methodology: VE will be estimated by 100 × (1 - IRR), where IRR is the calculated ratio of asymptomatic infection per 1000 person-years of follow-up in the active vaccine group to the corresponding infection in the placebo group. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method adjusted for surveillance time.
- Intercurrent events and missing data: Missing efficacy data will not be imputed in the main analyses.
- Reporting results: VE and the associated 2-sided 95% CIs derived using the Clopper-Pearson method adjusted for surveillance time will be provided.

6.3.3. Immunogenicity Endpoints

6.3.3.1. SARS-CoV-2 Reference-Strain Neutralizing Titers, SARS-CoV-2 SA-Variant Neutralizing Titers, and Full-Length S-Binding or S1-Binding IgG Levels (Phase 1)

6.3.3.1.1. Main Analyses

- Estimands:
  - GMTs/GMCs (Section 2.1).
  - GMFR from before Dose 3 to each subsequent time point, ie, 7 days and 1 month after Dose 3 (Section 2.1).
- Analysis set: Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.
- Analysis time points: At Dose 3 and 7 days and 1 month after Dose 3.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results (Section 5.2.3.1). GMFRs will be limited to participants with nonmissing values prior to Dose 3 and the subsequent time point. The GMFR will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later time point – earlier time point). 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 (Section 5.2.3.2).

- Intercurrent events and missing data: Concentrations below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: the GMTs/GMCs, GMFRs, and the associated 2-sided 95% CIs will be provided at each time point by initial vaccine and age group.

6.3.3.2. SARS-CoV-2 Reference-Strain Neutralizing Titers and SARS-CoV-2 SA-Variant Neutralizing Titers at 1 Month After Dose 3 vs SARS-CoV-2 Reference-Strain Neutralizing Titers at 1 Month After Dose 2 (Phase 1)

6.3.3.2.1. Main Analyses

- Estimands:
  - GMR of SARS-CoV-2 reference-strain neutralizing titers at 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers at 1 month after Dose 2 (Section 2.1).
  - GMR of SARS-CoV-2 SA-variant neutralizing titers at 1 month after Dose 3 to SARS-CoV-2 reference-strain neutralizing titers at 1 month after Dose 2 (Section 2.1).

- Analysis set: Phase 1 participants who received a third dose of BNT162b2 6 to 12 months after the second dose of either BNT162b1 or BNT162b2.

- Analysis time points: 1 month after Dose 3.

- Analysis methodology: GMRs will be limited to participants with nonmissing values at both time points and provided by initial vaccine and age group. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 SA-variant neutralizing titers at 1 month after Dose 3 minus reference-strain titers at 1 month after Dose 2 for each participant) and exponentiating the mean (Section 5.2.3.3). 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 (Section 5.2.3.3).

- Intercurrent events and missing data: Concentrations below the LLOQ or 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. Missing data will not be imputed.

- Reporting results: The GMRs and the associated 2-sided 95% CIs will be provided by initial vaccine and age group.

6.3.3.3. SARS-CoV-2 Neutralizing Titers, and Full-length S-Binding or S1-Binding IgG Levels (Phase 2/3)

6.3.3.3.1. Main Analyses

- Estimands:

  - GMTs/GMCs (Section 2.1).

  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).

- Analysis set: Dose 2 evaluable and all-available immunogenicity populations (Section 4).

- Analysis time points: 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination.

- Analysis methodology: GMs and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on Student's t-distribution, and then exponentiating the results Section 5.2.3.1). GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later time point – earlier time point). 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 (Section 5.2.3.2). Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers and full-length S-binding or S1-binding IgG levels after Dose 1 and after Dose 2.

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

- Reporting results: the GMTs/GMCs at each time point and GMFRs from before vaccination to each subsequent time point after vaccination, and the empirical RCDCs after Dose 1 and after Dose 2, will be provided.

6.3.3.3.2. Additional Exploratory Analyses

The above analyses will be performed by baseline SARS-CoV-2 status (positive or negative).

6.3.3.4. Serological Responses in Participants With Confirmed COVID-19, Confirmed Severe COVID-19, and SARS-CoV-2 Infection Without Confirmed COVID-19

The analyses described above for exploratory immunogenicity endpoints may be applied to the participants with confirmed COVID-19, confirmed severe COVID-19, and SARS-CoV-2 infection without confirmed COVID-19.

6.3.3.5. SARS-CoV-2 NTs for Any VOCs (Phase 3, Boostability and Protection Against Emerging VOCs)

GMs and associated 2-sided 95% CIs of any anti-VOC neutralizing titers will be provided at each time point for each group.

6.3.4. Additional Analysis

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point (Section 5.2.3.4).

The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” and each lot of “Process 2” will be summarized descriptively.

AEs and SAEs reported during the open-label follow-up period will be summarized separately for participants who were unblinded at the time of being eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, or no later than at approximately Visit 4. To account for different durations of follow-up time due to unblinding in the study, AEs and SAEs during the blinded follow-up period and open label follow-up period may be summarized as incidence rates adjusted by exposure time.

Exploratory analyses to investigate possible immunological correlates with efficacy, and characterization of infecting SARS-CoV-2 variants, may be conducted.

The cell-mediated immune response and additional humoral immune response parameters to the reference strain and SA will be summarized for the subset of participants with PBMC samples collected.

6.4. Subgroup Analysis

Subgroup analyses based on age, race, ethnicity, sex, country, and baseline SARS-CoV-2 status will be performed on all primary safety and efficacy endpoints (as supplemental analyses) for Phase 2/3.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

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

6.5.1.2. 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.

The number and proportion of participants with comorbidities that increase the risk for severe COVID-19 illness will be summarized by each vaccine group.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. 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 follow-up visits (1 month after the second dose), and who withdrew before each follow-up visit along with the reasons for withdrawal will be tabulated by vaccine group (according to randomized group assignment). 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.

Participants follow-up time after completion of vaccinations will be summarized by vaccine group.

6.5.2.2. Blood Samples for Assay

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

6.5.2.3. E-Diaries

The participants who were vaccinated and completed e-diaries after each dose will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1.1 and Section 6.1.1.2, the summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary, and transmitting the e-diary for any day in the required reporting period, by as-received vaccine group for each dose.

The safety population will be used.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

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

In addition, the relation of randomized vaccine to actual vaccine received will be presented as a cross tabulation of the actual vaccine received versus the randomized vaccine.

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

6.5.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification. 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. A summary will be provided for the interval between Dose 1 and 1 month after the second dose. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analyses

Local reaction, systemic event, AE, and SAE summaries and analyses are described under Primary Endpoint(s) (Section 6.1).

7. ANALYSES TIMING

7.1. Introduction of Interim Analysis

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, P[VE >30%|data]) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis can be found in Appendix 2.

- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is <5%. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint, and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.

- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, beta (0.700102, 1), is proposed for $\theta = (1\text{-VE})/(2\text{-VE})$. The prior is centered at $\theta = 0.4118$ (VE=30%), which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

Table 11 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 11. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine:placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 12 and Table 13 for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true VE=30%) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

Table 12. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 13. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of study intervention onwards.

Only the first primary endpoint will be analyzed at an IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints will be evaluated sequentially in the following order by the same method used for the evaluation of primary VE endpoints: (1) confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and (2) in all participants; (3) confirmed severe COVID-19 occurring from 7 days after the second dose in participants without evidence of infection and (4) in all participants; (5) confirmed severe COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and (6) in all participants.

Success thresholds for secondary VE endpoints will be appropriately chosen to control overall type I error at 2.5%. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

7.2. Interim Analyses and Summaries

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.

- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.

- IAs for efficacy after accrual of at least 62, 92, and 120 cases and futility after accrual of at least 62 and 92 cases.

- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.

- Descriptive analysis of immunogenicity and safety of "Process 1" and "Process 2" material, 1 month after Dose 2.

- Complete safety and immunogenicity analysis approximately 1 month after Dose 3 for Phase 3 participants included in the booster evaluation and approximately 1 month after Dose 2 for newly enrolled Phase 3 participants included in the BNT162b2$_{SA}$ evaluation.

- Analysis of efficacy against asymptomatic SARS-CoV-2 (determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT) when a sufficient number of cases have accrued to evaluate the objective(s).

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

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

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

7.2.1. Data Monitoring Committee

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

8. REFERENCES

1. Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

3. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990;131(2):373-5.

4. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16(3):219-42.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BLQ	below the level of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DBP	diastolic blood pressure
DMC	data monitoring committee
E1a, E1b, etc	identifier for vaccine-experienced participants (with a and b representing GMR and seroresponse estimands, respectively)
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
FiO_2	fraction of inspired oxygen
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HR	heart rate
IA	interim analysis
ICD	informed consent document
ICU	intensive care unit
IgG	immunoglobulin G
IND	indeterminate
IRC	internal review committee
IRR	illness rate ratio
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
N1a, N1b, etc	identifier for vaccine-naïve participants (with a and b representing GMR and seroresponse estimands, respectively)
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
NT	neutralizing titer
PaO_2	partial pressure of oxygen, arterial
PBMC	peripheral blood mononuclear cell
POS	probability of success
PT	preferred term
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RPSFT	rank-preserving structural failure time
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
S	spike protein
S1	spike protein S1 subunit
SA	South Africa
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
VE	vaccine efficacy
VOC	variant of concern
WBC	white blood cell
WHO	World Health Organization

Appendix 2. Details for Bayesian Design

Bayesian group sequential design will be implemented in the Phase 3 for this study.

Notation

(1) Let VE be vaccine efficacy, θ be the case rate (number of cases in the active vaccine group divided by the total number of cases), T_1 be the total person-time in the active vaccine group, T_0 be the total person-time in the placebo group, and r be the ratio of T_1 and T_0, ie, $r = T_1/T_0$. Note that $\theta = \frac{r(1-VE)}{r(1-VE)+1}$ and $VE = 1 - \frac{\theta}{r(1-\theta)}$.

(2) Let p be the posterior probability of VE greater than or equal to 30% given the observed data on subset of enrolled participants, ie:

$$p = \Pr(VE > 30\% \mid \text{observed data from subset of enrolled participants})$$

$$= \Pr\left(\theta < \frac{r(1-30\%)}{r(1-30\%)+1} \mid \text{observed data from subset of enrolled participants}\right)$$

Under the assumption that the numbers of cases in both vaccine groups, s_1 and s_0 for cases in the active vaccine group and cases in the placebo group, respectively, follow a Poisson distribution with parameter λ_1 (incidence rate) for the active vaccine group and λ_0 for the placebo group, we can assume that s_1 is binomially distributed with Binomial (s, θ), conditional on s, the total number of cases, and with $\theta = T_1 \lambda_1 / (T_1 \lambda_1 + T_0 \lambda_0)$.

A minimally informative beta prior, Beta(0.700102, 1) is selected as the prior distribution of θ. The prior distribution is chosen such that the mean is equal to 0.4118 corresponding to VE = 30% which can be considered pessimistic. Meanwhile, the prior allows for considerable uncertainty, ie, 95% credible interval for θ is (0.005, 0.964) corresponding to 95% credible interval, (-26.2, 0.995), for VE.

Decision Algorithm for Efficacy

At certain interim analysis and final analysis, let n be the total number of observed cases and n_v be the number of observed cases from the vaccine group. For beta-binomial model, the posterior distribution of θ will be derived as Beta($\alpha' = 0.700102 + n_v$, $\beta' = 1 + n - n_v$). At each interim and final analysis p will be used for efficacy decision making in the following way:

(a) At interim analyses, efficacy is declared if $p > 99.50\%$.

(b) At final analysis, efficacy is declared if $p > 98.60\%$.

In participants without evidence of infection prior to 7 days after the second dose, IAs will be performed after accrual of at least 62, 92, and 120 cases, and final analysis will be performed after accrual of at least 164 cases.

Based on the criterion (b), at final analysis, efficacy will be declared if there are less than or equal to 53 cases observed in the vaccine group among the total number of 164 cases.

Bayesian 95% credible interval for θ can be calculated using the 2.5th percentile and the 97.5th percentile of posterior distribution, ie, Beta(α'=0.700102 + n_v , β'=1 + n - n_v). Thus, the 95% credible interval for VE can be obtained correspondingly due to the relationship between VE and θ, where $VE = 1 - \frac{\theta}{r(1-\theta)}$.

Decision Algorithm for Futility

Let Y be the random variable for the number of cases in the vaccine group at the final analysis. At certain interim analysis given the total number of observed cases n and the number of observed cases from the vaccine group n_v, the posterior probability of success q can be expressed as:

q = Pr (Y ≤ 53 | observed data, ie, n and n_v, from subset of enrolled participants)

q can be calculated analytically using posterior predictive distribution of Y, ie, Beta-Binomial distribution with parameters (n', α', β'). The probability mass function of the posterior predictive distribution is:

$$\Pr(Y = y|n', \alpha', \beta') = \binom{n'}{y} \frac{B(y + \alpha',\ n' - y + \beta')}{B(\alpha', \beta')}$$

Thus the posterior probability of success at the interim analysis can be calculated as:

q = Pr (Y ≤ 53 – n_v | n' = 164 – n, α'=0.700102 + n_v , β'=1 + n - n_v)

At interim analyses, futility is declared if q < 5.0%.

Appendix 3. IRR and VE Derivation

COVID-19 Case Definitions

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

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

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

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

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

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

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a 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.

Surveillance Times

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

Endpoint's Associated Participant-Level Population	Start-of-Surveillance Time
Evaluable efficacy (7 days)	Dose 2 + 7 days
Dose 2 all-available efficacy	Dose 2 + 7 days
Evaluable efficacy (14 days)	Dose 2 + 14 days
Dose 2 all-available efficacy	Dose 2 + 14 days
Dose 1 all-available efficacy	Dose 1

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

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

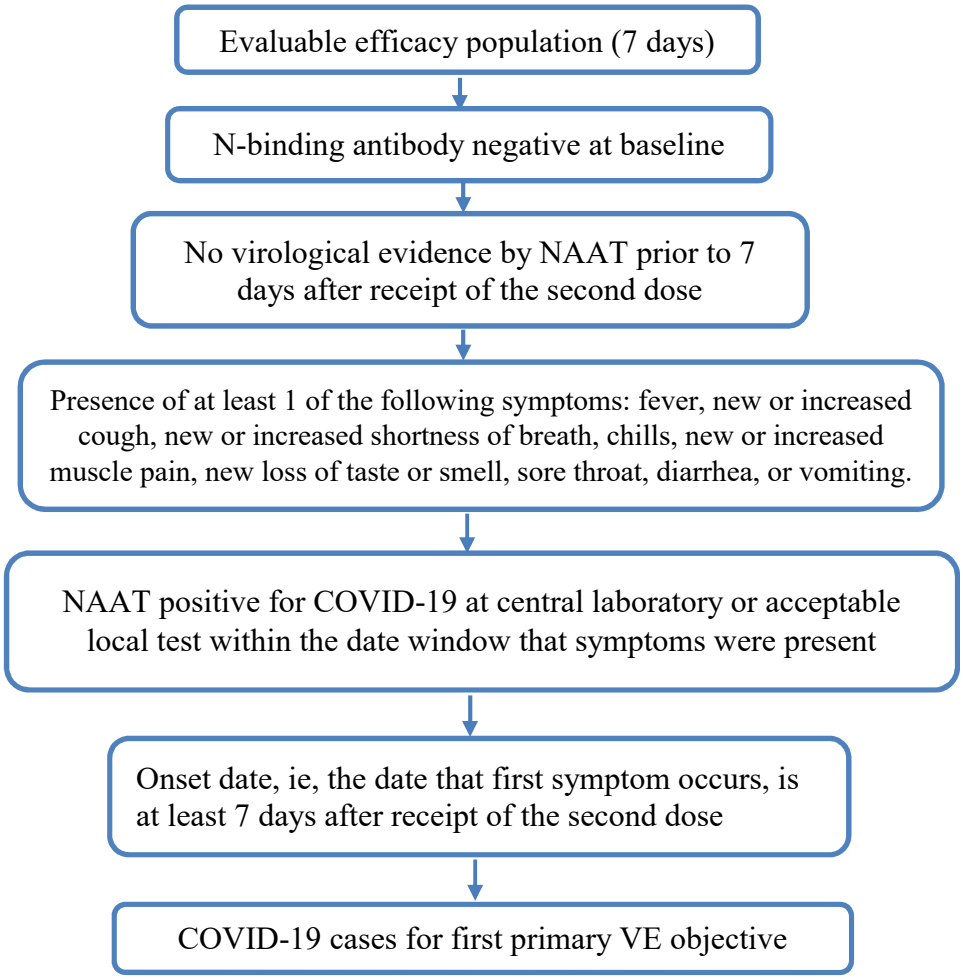
For descriptive assessment of exploratory endpoints of the COVID-19 incidence rate through the entire study follow-up period, the surveillance period is defined in the same way except that unblinding will not be considered as the end of the surveillance period.

Specific information regarding VE-related endpoint surveillance start and end times by endpoint will be provided in Analysis and Reporting Plan specification documents.

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

Flowchart

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



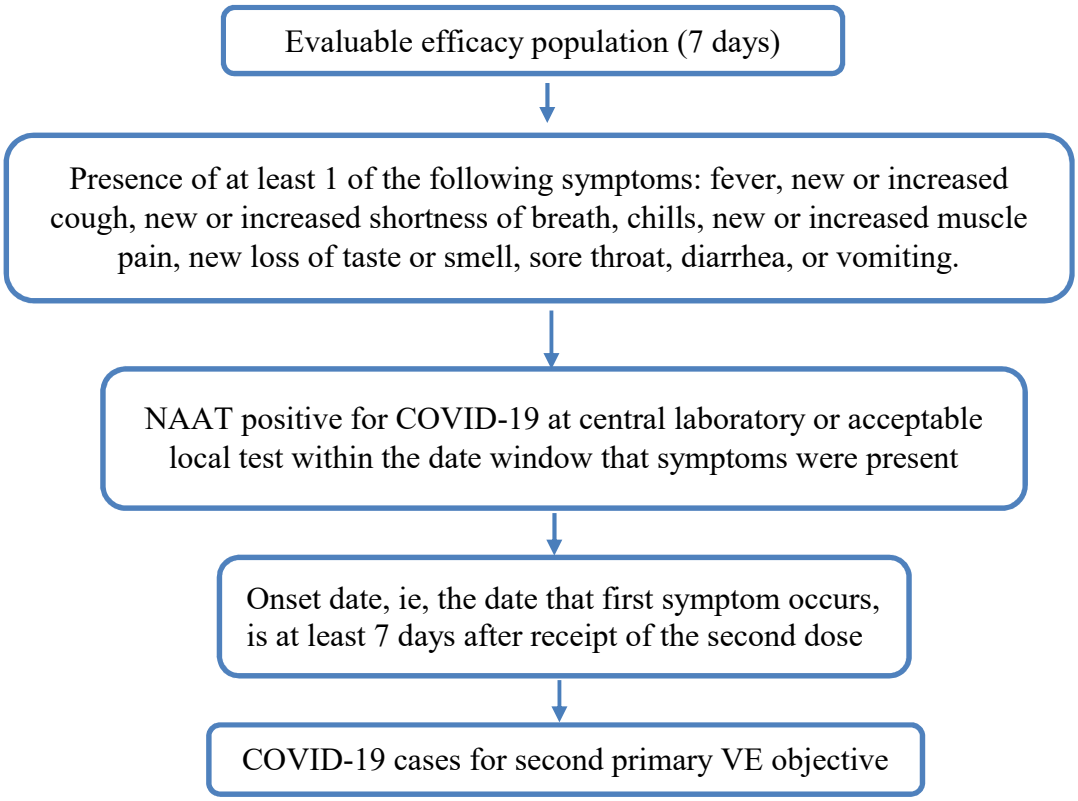
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

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

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

2. The flowchart for deriving the COVID-19 cases included below for the second primary endpoints in evaluable efficacy participants:



The flowcharts for the first 2 secondary vaccine efficacy endpoints are similar to the primary endpoints except that the case counting starts from 14 days after receipt of the second dose.

Appendix 4. Asymptomatic Case Based on N-Binding Antibody Seroconversion

Asymptomatic Case Definition

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

Surveillance Times

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

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

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

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

Appendix 5. Asymptomatic Case Based on Central Laboratory–Confirmed NAAT

Asymptomatic Case Definition

An asymptomatic case is defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it, in participants who are consented to participate in the asymptomatic surveillance and without (or with) serological or virological evidence of past SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.

Surveillance Times

The start-of-surveillance time is the start of the asymptomatic surveillance period.

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

- When the first positive NAAT occurs.
- When the last NAAT result is available.
- When the first COVID-19 symptom occurs.
- When the participant's asymptomatic surveillance period ends because the participant's participation in the study ended (withdrawal, death, trial completion, etc).
- When the participant has his or her first important protocol violation (only for analysis based on the evaluable efficacy population).