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: 3

Date: 02 Nov 2020

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216667

TABLE OF CONTENTS

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216668

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216669

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216670

LIST OF TABLES

APPENDICES

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216671

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.

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216672

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 • 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	SARS-CoV-2 neutralizing titers S1-binding IgG levels and RBD-binding IgG levels

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216673

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

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.
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).

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216674

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

Objectives[a]	Estimands	Endpoints
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
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.
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:	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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216675

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

Objectives[a]	Estimands	Endpoints
	100 × (1 – IRR) [ratio of active vaccine to placebo]	
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 NAA.T
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.
Exploratory		
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, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination.	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study.		• N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19		• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
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]		• All safety endpoints described above • SARS-CoV-2 neutralizing titers

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216676

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;
- 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.

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216677

- 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.

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216678

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 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67). A random sample of 250 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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216679

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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Safety Endpoints

For all participants in Phase 1, and a subset of at least 6000 participants randomized in Phase 2/3, receiving at least 1 dose of study intervention, 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/tiredness, 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.

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216680

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216681

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.

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FDA-CBER-2021-5683-0216682

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/tiredness, 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/tiredness	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe fatigue.
Chills	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe chills.
New or worsened muscle pain	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe new or worsened muscle pain.
New or worsened joint pain	Does not interfere with activity.	Some interference with activity.	Prevents daily routine activity.	Emergency room visit or hospitalization for severe new or worsened joint pain.

Abbreviation: IV = intravenous.

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216683

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.

The primary endpoint "AEs from Dose 1 to 1 month after the second dose" and other AE endpoints will be summarized by SOC and PT at the participant level.

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

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

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216684

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).

The safety endpoint "SAEs from Dose 1 to 6 months after the second dose" will be summarized by SOC and PT at the participant level.

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216685

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

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
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

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216686

Table 8. Laboratory Abnormality Grading Scale

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. 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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216687

Phase 2/3

In participants with no serological or virological evidence of past SARS-CoV-2 infection, 12 to 15 years of age and 16 to 25 years of age complying with the key protocol criteria (evaluable participants) 1 month after Dose 2, below is the secondary immunogenicity endpoint for Phase 2/3:

- SARS-CoV-2 neutralizing titers.

3.2.1.1. Neutralizing Titers

Titers 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.

3.2.1.2. IgG Concentrations

Results will be reported as IgG concentrations. IgG concentrations 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.

To support the secondary immunogenicity endpoints, the GMTs or concentrations at all time points, GMFR from before vaccination to each subsequent time point after vaccination, and proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination will be calculated and summarized by vaccine group.

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).

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216688

- 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).

3.3. Exploratory Endpoints

3.3.1. Immunogenicity Endpoints (for Phase 2/3 Only)

In participants complying with the key protocol criteria (evaluable 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.

- S1-binding IgG levels and/or RBD-binding IgG levels.

- N-binding antibody.

- SARS-CoV-2 detection by NAAT.

3.3.2. 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.

- All safety endpoints described above, 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.”

3.4. Baseline and Other Variables

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

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216689

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, and a subset of at least 6000 in Phase 2/3, an e-diary will be considered transmitted if any data for the local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all 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).
- 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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216690

- 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 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.
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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216691

Population	Description
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.
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.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

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

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216692

The assessment for the primary analysis will be based on posterior probability using a beta-binomial model (see Appendix 2 for details).

5.1.2. Immunogenicity Hypothesis

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.

5.1.3. Sample Size

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.

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.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 250 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 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% 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).

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216693

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 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	0.623	-0.2	200	90.8%

Abbreviation: GMR = geometric mean ratio.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 1, N=12). Calculation may be updated if additional information becomes available to better estimate the standard deviation.

b. At 0.05 alpha level (2-sided).

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=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>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
7.00%	0.58	0.96	>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

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216694

5.1.4. Multiplicity Considerations

For Phase 1, there is no hypothesis testing. 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).

5.2. 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 Continuous Data

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

5.2.2.1. Geometric Means

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.

090177e19568e83f\Approved\Approved On: 02-Nov-2020 21:20 (GMT)

FDA-CBER-2021-5683-0216695

5.2.2.2. 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.

5.2.2.3. 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.

5.2.2.4. 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.

5.2.2.5. 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.

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FDA-CBER-2021-5683-0216696

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 6.1.2.1.2.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Safety Endpoints

The safety analyses are based on the safety population. 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 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.

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FDA-CBER-2021-5683-0216697

- 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/tiredness, 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 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.

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FDA-CBER-2021-5683-0216698

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, and from Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2 (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.
- 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.

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FDA-CBER-2021-5683-0216699

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, and from Dose 1 to 7 days after the second dose for the first 360 participants randomized in Phase 2 (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.
- 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 1 to 6 months/7 days after the second dose 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.

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FDA-CBER-2021-5683-0216700

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

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

6.1.2.1.1. 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).

6.1.2.1.2. 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.[3] 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.

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FDA-CBER-2021-5683-0216701

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.

Efficacy could also be assessed over a longer time period using time-to-event data analysis methods (eg, Cox model) 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.

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FDA-CBER-2021-5683-0216702

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 5.2.2.1). 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 5.2.2.2). 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 5.2.2.5).

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FDA-CBER-2021-5683-0216703

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 5.2.2.1). 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 5.2.2.2). 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 5.2.2.5).

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FDA-CBER-2021-5683-0216704

6.2.1.3. GMR of SARS-CoV-2 Neutralizing Titer to 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 5.2.2.3). 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 5.2.2.3).
- 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. GMR of SARS-CoV-2 Neutralizing Titers in Participants 12 to 15 Years of Age to 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.

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FDA-CBER-2021-5683-0216705

- 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 5.2.2.3).

- 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.

6.2.2. 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 6.1.2.1.1).

- 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 6.1.2.1.1).

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FDA-CBER-2021-5683-0216706

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 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 6.1.2.1.1).
- 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 6.1.2.1.1).

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 and all-available efficacy populations (Section 4).

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FDA-CBER-2021-5683-0216707

- 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.

6.3. Exploratory Endpoints

6.3.1. Immunogenicity Endpoints (for Phase 2/3 Only)

6.3.1.1. SARS-CoV-2 Neutralizing Titers, and S1-Binding IgG Levels and RBD-Binding IgG Levels

6.3.1.1.1. Main Analyses

- Estimands:
  - GMTs/GMCs (Section 2.1).
  - GMFR from before vaccination to each subsequent time point after vaccination (Section 2.1).
  - Percentage of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters.
- Analysis set: Dose 1 and 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.

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FDA-CBER-2021-5683-0216708

- 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 5.2.2.1). 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 5.2.2.2). Percentages of participants with antibody levels ≥ predefined threshold(s) for SARS-CoV-2 serological parameters will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method).

- 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, GMFRs from before vaccination to each subsequent time point after vaccination, and the percentages of participants with antibody levels ≥ predefined threshold(s) for baseline SARS-CoV-2 serological parameters and the associated 2-sided 95% CIs from before vaccination to each time point after vaccination will be provided.

6.3.1.1.2. Additional Exploratory Analyses

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

6.3.1.2. N-Binding Antibody

- Estimands:
  - Percentage of participants with seroconversion by N-binding antibody.
  - Analysis set: Dose 1 and 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: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed.
- Reporting results: Percentages of participants with seroconversion by N-binding antibody will be calculated with the associated 2-sided 95% CIs (Clopper-Pearson method) at baseline and each time point after vaccination.

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FDA-CBER-2021-5683-0216709

6.3.1.3. 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.

6.3.2. 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 5.2.2.4).

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.

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

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.

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FDA-CBER-2021-5683-0216710

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.

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FDA-CBER-2021-5683-0216711

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.

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FDA-CBER-2021-5683-0216712

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.

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FDA-CBER-2021-5683-0216713

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.

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FDA-CBER-2021-5683-0216714

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 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.

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FDA-CBER-2021-5683-0216715

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FDA-CBER-2021-5683-0216716

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
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
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable

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FDA-CBER-2021-5683-0216717

Abbreviation	Term
NAAT	nucleic acid amplification test
PaO_2	partial pressure of oxygen, arterial
POS	probability of success
PT	preferred term
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization

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FDA-CBER-2021-5683-0216718

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 . $= \frac{r(1-VE)}{r(1-VE)+1}$ 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:

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

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

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.

FDA-CBER-2021-5683-0216719

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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%.

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FDA-CBER-2021-5683-0216720

Appendix 3. IRR and VE Derivation

COVID-19 Case Definition

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.

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FDA-CBER-2021-5683-0216721

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 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

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FDA-CBER-2021-5683-0216722

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 and etc.
- When the participant has first important protocol violation.

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.

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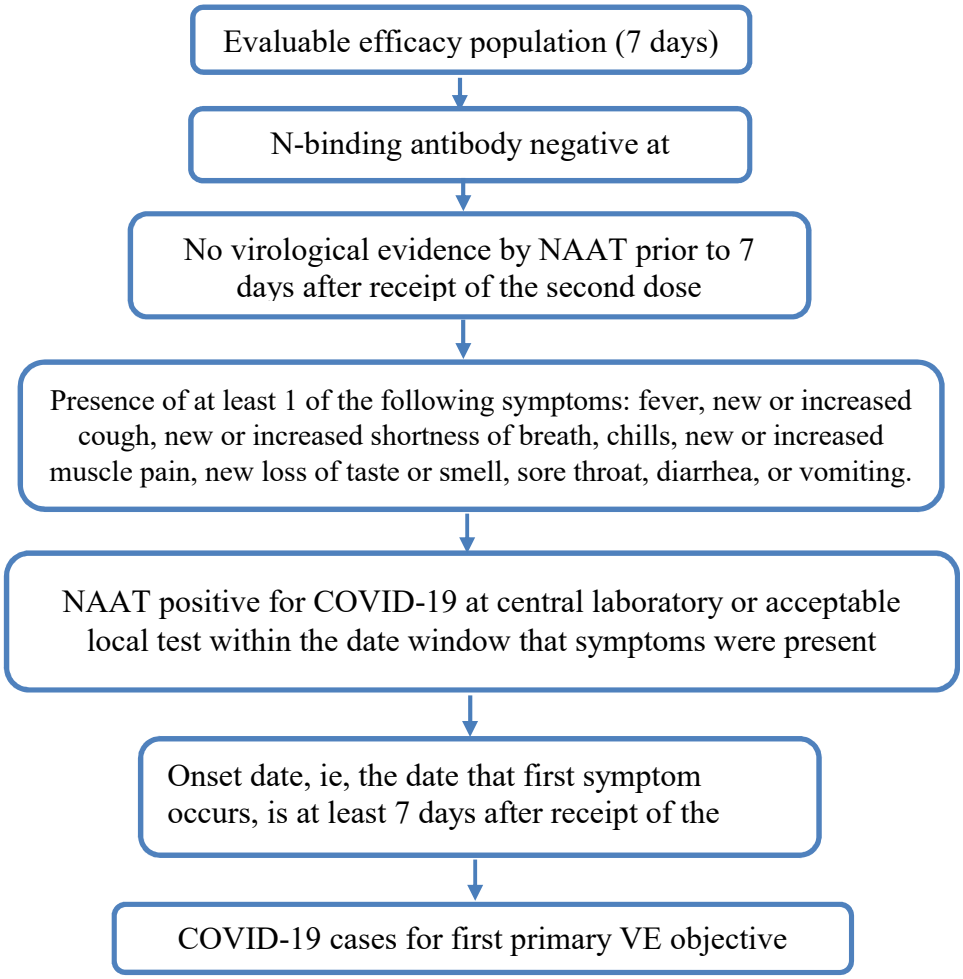
FDA-CBER-2021-5683-0216723

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)

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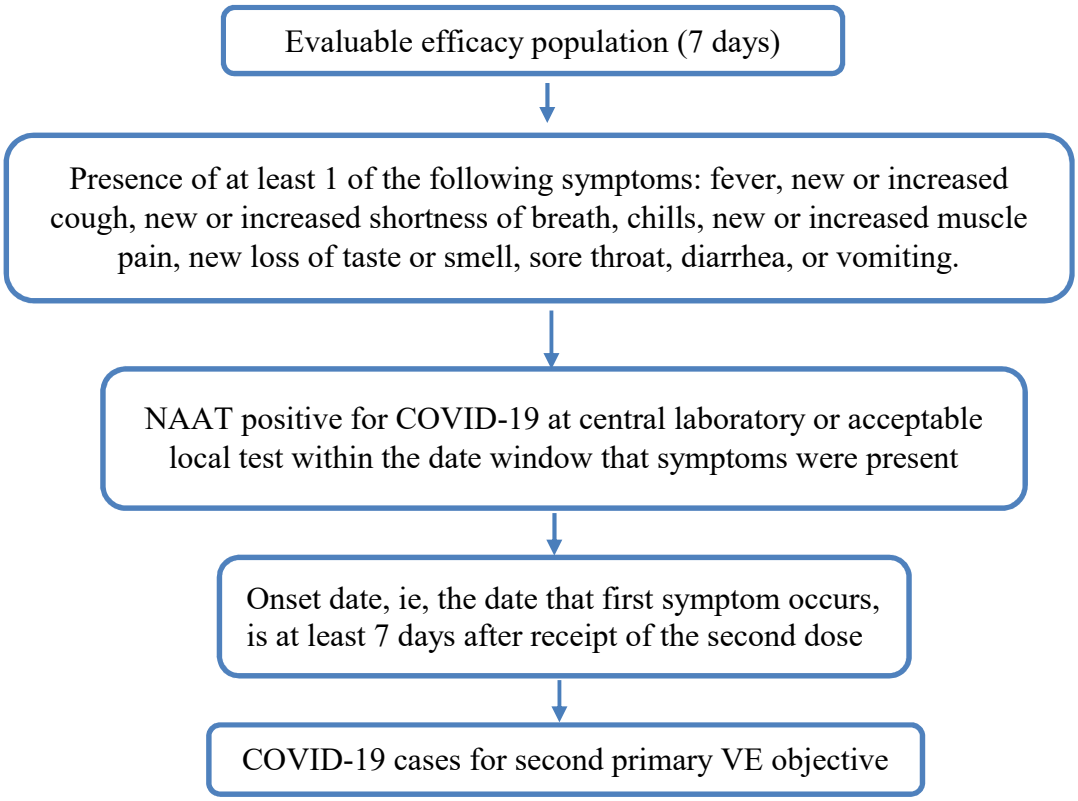
FDA-CBER-2021-5683-0216724

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.

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