Protocol C4591031 – Substudy A

A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 – SUBSTUDY A

Statistical Analysis Plan (SAP)

Version: 2

Date: 16 August 2022

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 30 Jun 2021	Protocol Amendment 1, 27 May 2021	N/A	N/A
2/ 16 Aug 2022	Protocol Amendment 10, 22 Jul 2022	• Because of changes in access to and availability of BNT162b2 in the real world, and for participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program. • Interim analyses are no longer needed every 2 months as this study has been unblinded. This will allow the team to deliver the analysis if required for regulatory purposes. • Protocol clarification.	• Added language to permit early discontinuation of participants in Section 2.2. • Modified Section 7.1 and Section 7.2. Removed the efficacy and safety analyses when all participants completed blinded follow-up and added that additional analyses may be conducted if required for regulatory purposes. Removed the requirement to conduct interim analyses every 2 months. • Deleted the language on efficacy against asymptomatic SARS-CoV-2 infection (Section 2.1, Table 2; Section 3.2.1; Section 6.2.1.3; and Appendix 3). Modified Section 6.3.1.1.1 to remove analyses on evaluable efficacy population.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in C4591031 – Substudy A. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

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

In the primary safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the efficacy objectives are based on the evaluable efficacy population (see Section 4 for definition). These estimands estimate VE 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 (mITT) population. Missing laboratory results will not be imputed for the efficacy endpoints.

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary Efficacy	**Primary Efficacy**	**Primary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed COVID-19 occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • AEs from the booster dose to 1 month after the booster dose • SAEs from the booster dose to 6 months after the booster dose	• AEs • SAEs
Secondary Efficacy	**Secondary Efficacy**	**Secondary Efficacy**
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

Table 2. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on FDA definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with no serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
To describe the efficacy of a booster dose of BNT162b2 against confirmed severe COVID-19 (based on CDC definition) occurring from 7 days after the booster dose through the blinded follow-up period in participants with and without evidence of past SARS-CoV-2 infection	In participants complying with the key protocol criteria (evaluable participants) and with or without serological or virological evidence (prior to 7 days after receipt of the booster dose) of past SARS-CoV-2 infection: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up
Exploratory		
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received the BNT162b2 booster dose	In participants who received BNT162b2 at the booster vaccination (at initial randomization and subsequently): Incidence per 1000 person-years of follow-up	Confirmed COVID-19 incidence per 1000 person-years of the entire study follow-up period

2.2. Study Design

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization will be enrolled, and participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization will be stratified by age, such that approximately 60% of participants enrolled will be ≥16 to 55 years of age and approximately 40% of participants >55 years of age. Approximately 10,000 participants will be randomized in the study. Assuming a 15% nonevaluable rate, there will be approximately 4250 evaluable participants in each group.

Participants who are randomized to receive placebo at the booster vaccination visit will be offered the opportunity to receive BNT162b2 if indicated by the outcome of the interim analyses further detailed in Section 7. The timing of this booster vaccination will also be informed by the outcome of the interim analyses detailed in Section 7.

The study may be terminated early, for reasons including (but not limited to) changes in access to and availability of BNT162b2 in the real world, which reduces the value of participant involvement and observation in this clinical trial. Furthermore, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Efficacy Endpoint

- Confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

3.1.2. Safety Endpoints

- AEs from the booster dose to 1 month after the booster dose
- SAEs from the booster dose to 6 months after the booster dose

3.1.2.1. Adverse Events

AEs will be assessed from the time of informed consent through Visit 2 (approximately 1 month after the booster vaccination), and from Visit 101 to Visit 102 (approximately 1 month after participants who originally received placebo are administered BNT162b2). AEs will be categorized according to MedDRA terms.

The primary safety endpoints will be summarized by SOC and PT at the participant level.

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

AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

A 3-tier approach will be used to summarize AEs from booster vaccination through Visit 2. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

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

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

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

3.1.2.2. Serious Adverse Events

SAEs will be assessed from the time of informed consent to Visit 3 (approximately 6 months after the booster vaccination), and from Visit 101 to 103 (approximately 6 months after participants who originally received placebo are administered BNT162b2). SAEs will be categorized according to MedDRA terms.

The primary safety endpoints will be summarized by SOC and PT at the participant level. Additionally, the SAEs will be listed.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

- Confirmed severe COVID-19 (based on FDA definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

- Confirmed severe COVID-19 (based on CDC definition) incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up

3.3. Exploratory Endpoints

3.3.1. Efficacy Endpoint

- Confirmed COVID-19 incidence per 1000 person-years of the entire study follow-up period

3.4. Baseline and Other Variables

Measurements or samples collected prior to booster vaccination at Visit 1 are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at booster vaccination (in years), sex (male or female), BMI, race (Black/African American, American Indian, or Alaska 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.

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 booster vaccination 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 may increase the risk for severe COVID-19 illness will be categorized based on medical history terms.

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

3.4.2. Prior/Concomitant Vaccines and Concomitant Medications

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

- Any vaccinations received from 28 days prior to study enrollment until 28 days following administration of the last study intervention.
- Prohibited medications listed in Protocol Section 6.8.1 will be recorded to include start and stop dates, name of the medication, dose, unit, route, and frequency.

Prior and concomitant vaccines and concomitant medications will be coded using WHO DDE.

3.5. Safety Endpoints

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.
Evaluable efficacy	All eligible randomized participants who receive the booster vaccination as randomized and have no other important protocol deviations as determined by the clinician.

Population	Description
All-available efficacy (mITT)	All randomized participants who receive at least 1 dose of the study intervention.
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 efficacy, eg, participant receipt of a medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they received.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

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

The majority of Pfizer staff will be blinded to study intervention allocation. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The study will be unblinded to all sponsor/Pfizer staff at a time informed by the outcome of the interim analyses as detailed in Section 7. Further details can be found in Protocol Section 10.7.6.2.

5.1. Hypotheses and Decision Rules

All objectives in this substudy are descriptive. No hypothesis testing is planned.

No multiplicity adjustment is applied for the study as there is no statistical hypothesis.

5.2. General Methods

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 Endpoints

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 method).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

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

5.2.2. Analyses for Count Data

Descriptive statistics for count data are incidence rate, the numerator (number of events observed) and the denominator (total person-years of follow-up) used in the incidence rate calculation, and the 95% CIs where applicable.

The exact 95% CI for incidence rates for each group will be computed using the method of Ulm[3] based on the link between the chi-square distribution and the Poisson distribution.

5.2.3. Analyses for Continuous Endpoints

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

5.3. Methods to Manage Missing Data

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

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Vaccine Efficacy Endpoint

6.1.1.1. Confirmed COVID-19 Incidence From 7 Days After the Booster Dose per 1000 Person-Years of Blinded Follow-up

6.1.1.1.1. Main Analysis

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster 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 booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).
- Analysis time points: At interim analyses and at the end of the surveillance period (blinded follow-up).
- Analysis methodology: VE 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 from 7 days after the booster dose (see Appendix 2 for details on the derivation of IRR and VE). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.
- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.1.1.1.2. Supplementary Analyses

A descriptive summary of VE over different time intervals (ie, through 2 months, from 2 to 4 months, and from 4 to 6 months after the booster dose, etc.), along with the associated 2-sided 95% CI, will also be calculated using the same method.

VE by time between Dose 2 of the primary vaccination series and the booster dose (eg, 6-8 months, 8-10 months, 10-12 months after Dose 2) will also be summarized descriptively. Kaplan-Meier cumulative incidence curves will be provided.

6.1.2. Safety Endpoints

6.1.2.1. Adverse Events

6.1.2.1.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the booster dose to 1 month after the booster dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Booster dose to 1 month after the booster dose.
- Analysis methodology: Descriptive statistics (Section 5.2.1) and an additional 3-tier approach (Section 3.1.2.1).
- Intercurrent events and missing data: Partial AE start 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. Under this approach, AEs are classified into 1 of 3 tiers (Section 3.1.2.1). 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 the SOC. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AEs, by each SOC and each PT within the SOC for each vaccine group.

6.1.2.1.2. Supplementary Analyses

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose) will also be summarized for each vaccine group. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.2.2. Serious Adverse Events

6.1.2.2.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from the booster dose to 6 months after the booster dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Booster dose to 6 months after the booster dose.

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

6.2. Secondary Endpoint(s)

6.2.1. Secondary Efficacy Endpoints

6.2.1.1. Confirmed Severe COVID-19 (Based on FDA Definition) Incidence From 7 Days After the Booster Dose per 1000 Person-Years of Blinded Follow-up

6.2.1.1.1. Main Analyses

- Estimands:
  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
  - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on FDA definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).
- Analysis methodology: VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed severe COVID-19 illness rate (based on FDA definition) per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose (see Appendix 2 for details on the derivation of IRR and VE). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.
- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.2.1.2. Confirmed Severe COVID-19 (Based on CDC Definition) Incidence From 7 Days After the Booster Dose per 1000 Person-Years of Blinded Follow-up

6.2.1.2.1. Main Analyses

- Estimands:
    - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
    - 100 × (1 – IRR) [ratio of confirmed severe COVID-19 illness (based on CDC definition) from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the booster dose) for the active vaccine group to the placebo group (Section 2.1)].
- Analysis set: Evaluable efficacy and all-available efficacy (mITT) populations (Section 4).
- Analysis time point: End of the surveillance period (blinded follow-up).
- Analysis methodology: VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed severe COVID-19 illness rate (based on CDC definition) per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the booster dose (see Appendix 2 for details on the derivation of IRR and VE). The 2-sided 95% CI for VE will be provided using the Clopper-Pearson method adjusting for surveillance time.
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.
- Reporting results: The point estimate of VE and the associated 2-sided 95% CI.

6.3. Exploratory Endpoints

6.3.1. Vaccine Efficacy Endpoint

6.3.1.1. Confirmed COVID-19 Incidence per 1000 Person-Years of the Entire Study Follow-up Period

6.3.1.1.1. Main Analyses

- Estimand:
    - Incidence of confirmed COVID-19 illness from 7 days after the booster dose per 1000 person-years of the entire study follow-up period in participants who received BNT162b2 at the booster vaccination at initial randomization and subsequently, respectively (Section 2.1).
- Analysis set: All-available efficacy (mITT) population (Section 4). For participants who were randomized to the placebo group and subsequently received BNT162b2, the time of receipt of BNT162b2 will be considered as the baseline. All rules for determining the all-available efficacy (mITT) population will be similarly applied.
- Analysis time point: End of the surveillance period.
- Analysis methodology: Incidence rate (per 1000 person-years of follow-up) and exact 2-sided 95% CI based on Poisson distribution (Section 5.2.2) for confirmed COVID-19 illness from 7 days after the booster vaccination will be provided for participants who received BNT162b2 at initial randomization and subsequently. Kaplan-Meier cumulative incidence of COVID-19 cases over time will be plotted.
- Intercurrent events and missing data: Missing efficacy data (symptom is present without laboratory testing data) will not be imputed.
- Reporting results: Incidence rate and the associated 2-sided 95% CIs and Kaplan-Meier cumulative incidence curves will be provided.

6.4. Subgroup Analysis

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

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age, 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 an 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 may increase the risk for severe COVID-19 illness will be summarized by each vaccine group.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received the booster vaccination, who completed the follow-up visits, and who withdrew from the study, 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.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving the booster dose, as well as the time between the booster dose and the doses of BNT162b2 prior to randomization, 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 will be presented.

6.5.4. Prior/Concomitant Vaccination and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the ATC 4th-level classification. All vaccines received within 28 days prior to study enrollment until 28 days following administration of the last study intervention will be listed. The number and percentage of participants receiving each concomitant vaccine after the booster vaccination will be tabulated by vaccine group. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

6.6. Safety Summaries and Analyses

AE and SAE summaries and analyses are described under Primary Endpoint(s) in Section 6.1.

7. INTERIM ANALYSES

7.1. Introduction

Interim efficacy analyses were originally planned to be performed every 2 months by an unblinded statistical team to inform the timing of administration of BNT162b2 to those originally assigned to the placebo group. This substudy has been unblinded after the first interim analysis as informed by the outcome of the analysis; follow-up interim analyses are no longer applicable. The first interim analysis was performed after all participants reached 2 months of blinded follow-up. The final efficacy analyses to assess the primary and secondary efficacy objectives are planned to be conducted using complete blinded follow-up period data.

At each interim analysis, the following 2 estimates of VE will be obtained: (1) VE of the BNT162b2 booster group relative to the nonbooster group (placebo), which is the primary estimand defined for this substudy and directly estimable using the data observed in this substudy; and (2) VE of the nonbooster group (received a primary series of 2 doses of BNT162b2 approximately 6 months prior to enrollment in this study and did not receive the BNT162b2 booster) relative to an unvaccinated population (never received the BNT162b2 primary series, not observable in this study). These estimates will be obtained using the following derivations.

Let VE_{12} be the VE of the BNT162b2 booster group relative to the nonbooster group, VE_1 be the VE of the BNT162b2 booster group relative to an unvaccinated population, VE_2 be the VE of the nonbooster group relative to an unvaccinated population, $/R_1$ be the incidence rate of COVID-19 illness in the BNT162b2 booster group, $/R_2$ be the incidence rate of COVID-19 illness in the placebo booster group, and $/R_0$ be the nonobservable incidence rate in the unvaccinated population.

(1) VE_{12} can be estimated by observed $/R_1$ and $/R_2$ in the study as $VE_{12} = 1 - \frac{IR1}{I_2}$;

Since $VE_1 = 1 - \frac{IR1}{IR_0}$, $VE_2 = 1 - \frac{IR2}{IR_0}$,

(2) VE_2 can then be estimated by observed $/R_1$ and $/R_2$ in the study and an assumed VE_1 as

$VE_2 = 1 - \frac{IR_2(1-VE_1)}{IR_1}$.

Although VE_1 is also not observable from the study, it is expected that VE after the booster dose will be similar to that after the first 2 vaccine doses. Based on the results of the updated efficacy analyses from Study C4591001, the VE from 7 days to 2 months, from 2 to 4 months, and from 4 to 6 months after Dose 2 were approximately 96%, 90%, and 84%, respectively. After 6 months, a 6% drop in VE every 2 months will be assumed. These assumed values of VE_1 will be used to estimate VE_2 at the interim analyses.

If the point estimate of VE_2 (nonbooster group relative to unvaccinated population) in a 2-month interval (ie, 7 days to 2 months, 2 to 4 months, etc.) at an interim analysis is <60%, the study will be unblinded, and the placebo group participants may receive BNT162b2 earlier than approximately 175 days after the vaccination at Visit 1. If VE_2 remains ≥60% at the interim analyses, all participants may remain blinded in the study and placebo recipients may not be offered BNT162b2 booster until the 12-month visit. In addition, the placebo group participants may not receive BNT162b2 as part of the study if VE_2 is ≥60% at the final analysis.

7.2. Analysis Timing

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

- Interim efficacy analyses after all participants reach 2 months of blinded follow-up
- Efficacy and safety analysis at the end of the study
- Additional analyses may be conducted if required for regulatory purposes

7.3. Data Monitoring Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

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

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

- At the time of the planned interim analyses, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

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

8. REFERENCES

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

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

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

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
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
FiO_2	fraction of inspired oxygen
HR	heart rate
ICD	informed consent document
ICU	intensive care unit
IRR	illness rate ratio
IWR	interactive Web-based response
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
PaO_2	partial pressure of oxygen, arterial
PT	preferred term
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation as measured by pulse oximetry
VE	vaccine efficacy
WHO DDE	World Health Organization Drug Dictionary Enhanced

Appendix 2. IRR and VE Derivation

COVID-19 Case Definition

Definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered as follows (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 positive SARS-CoV-2 NAAT 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.

- Confirmed severe COVID-19 (FDA definition; listed at https://www.fda.gov/media/139638/download): 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.

Confirmed severe COVID-19 (CDC definition; listed at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html): confirmed COVID-19 and presence of at least 1 of the following:

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

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

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	Booster dose + 7 days
All-available efficacy (mITT)	Booster dose + 7 days

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

- When the first COVID-19 case occurs.
- When the end of the study for the participant occurs due to, eg, withdrawal, death, or trial completion, etc.

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

- When the participant is unblinded at the time informed by the outcome of the interim analyses for receipt of BNT162b2 or other reasons.

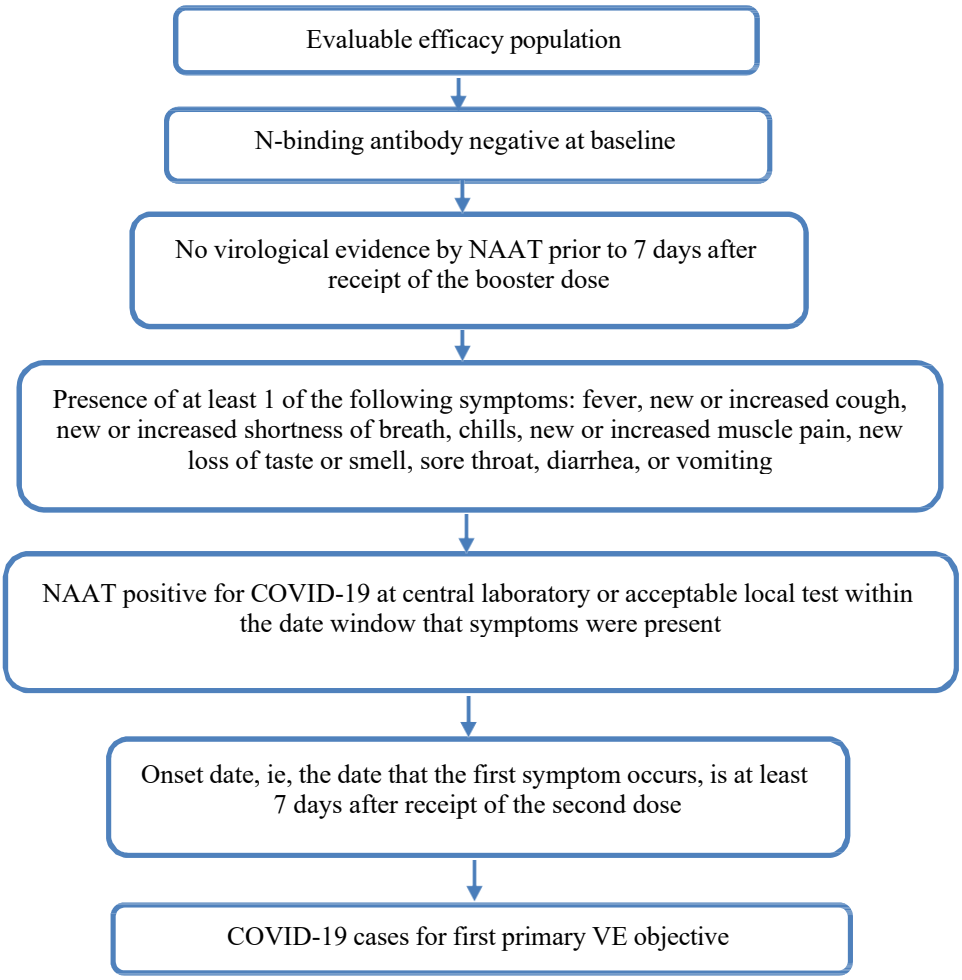
For descriptive assessment of exploratory endpoints of COVID-19 incidence rate through the entire study follow-up period, the surveillance period is defined the same way except that unblinding will not be considered as the end of the surveillance period.

Specific information regarding VE-related endpoint surveillance start and end times by endpoint will be provided in the analysis and reporting plan specification documents.

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

Flowchart

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



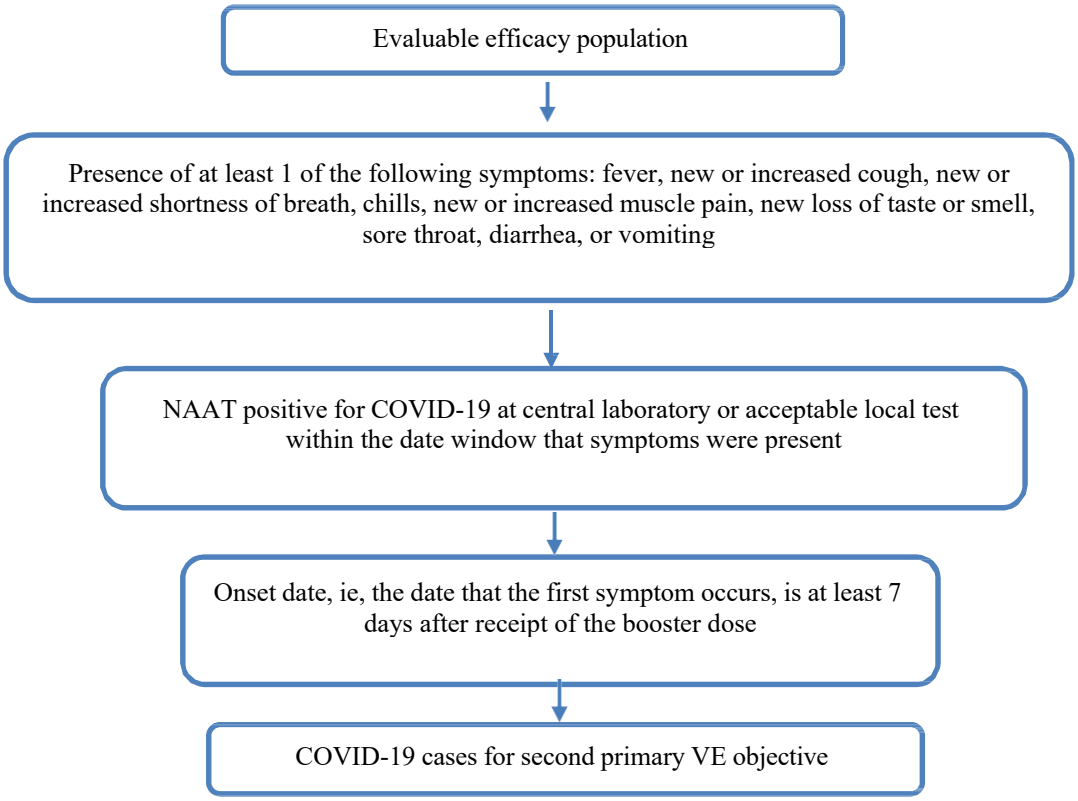
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

a. Cepheid Xpert Xpress SARS-CoV-2

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

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

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



Document Approval Record

Document Name:	C4591031 Sub Study A Statistical Analysis Plan V2 Clean Copy, 16Aug2022
Document Title:	A PHASE 3 MASTER PROTOCOL TO EVALUATE ADDITIONAL DOSE(S) OF BNT162b2 IN HEALTHY INDIVIDUALS PREVIOUSLY VACCINATED WITH BNT162b2 - SUBSTUDY A

Signed By:	Date(GMT)	Signing Capacity
PPD	16-Aug-2022 16:41:54	Final Approval