Protocol C4591030

A PHASE 3, RANDOMIZED, OBSERVER-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF BNT162b2 WHEN COADMINISTERED WITH SEASONAL INACTIVATED INFLUENZA VACCINE (SIIV) IN ADULTS 18 THROUGH 64 YEARS OF AGE

Statistical Analysis Plan
(SAP)

Version: 3

Date: 20 Oct 2022

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 28 Jan 2022	Protocol amendment 1 22 Dec 2021	N/A	N/A
2/ 06 Apr 2022	Protocol amendment 2 09 Mar 2022	Implemented the changes made in protocol amendment 2.	1. The study design has been updated to replace the third dose (booster) of BNT162b2 with a fourth dose (booster) of BNT162b2 (to enroll participants who had the third dose rather than the second dose). The text, "…timing of the second dose of BNT162b2 prior to Visit 1" was removed from Subset Analyses (Section 6.4). The text, "…timing of the second dose of BNT162b2 prior to Visit 1" in Section 6.5.1.1 was updated to "timing from the third dose…" due to this design change. 2. Stratification factors have been updated to remove timing of the second dose of BNT162b2 prior to Visit 1, and to add stratification by history of a prior positive SARS-CoV-2 test. 3. The linear regression model for primary immunogenicity endpoints has been updated to include evidence of SARS-CoV-2 infection as 1 of the factors (removing timing from the second dose at Visit 1). 4. In Section 3.1.1.4, added confirmed COVID-19 diagnosis or positive SARS-CoV-2 test result (by NAAT or rapid antigen test) as an AESI per PA2. 5. Definitions of analysis populations in Section 4 was updated per PA2.
		To correct a typographical error in the previous version.	Added "≥" in Section 4, the third paragraph, "An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population."

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
3/ 20 Oct 2022	N/A	Implemented the changes made in the decision log (based on clinical and statistical consideration, refining the definition and analysis of evaluable BNT162b2 immunogenicity population).	1. Added, "have no reported COVID-19 or new SARS-CoV-2 infection after Visit 1 and through 1 month after the BNT162b2 vaccination (Visit 2 for the coadministration group and Visit 3 for the separate-administration group)" in the definition of the evaluable BNT162b2 immunogenicity population in Section 4. 2. Replaced "evidence of SARS-CoV-2 infection" with "corresponding baseline assay results" from the primary analysis model in Sections 5.2.2.1, 6.1.2.1, and 6.1.2.2. 3. In Section 6.4 Subset Analyses, replaced "without evidence of SARS-CoV-2 infection through 1 month after BNT162b2 vaccination" with "baseline SARS-CoV-2 status (based on N-binding antibody results at Visit 1 before vaccination and medical history of SARS-CoV-2)."
		Clarification	In Section 6.2.1.1.1, added clarification that "before vaccination" refers to Visit 1 for the coadministration group and Visit 2 for the separate-administration group.
		Clarified the supplemental analyses	Moved the designation of "without evidence of infection" to newly added Section 6.1.2.1.2 (Supplemental Analysis).
		Timing from BNT162b2 is more clinically relevant to the BNT endpoint.	In Section 6.5.1.1, revised "timing of the third dose of BNT162b2 prior to Visit 1" to "timing of the third dose of BNT162b2 prior to BNT162b2 vaccination received during the study."

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4591030. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

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

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

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity populations (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

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

Objectives	Estimands	Endpoints
Primary Safety Objective:	**Primary Safety Estimands:**	**Primary Safety Endpoints:**
To describe the safety profile of BNT162b2 when coadministered with SIIV	In participants receiving 1 dose of BNT162b2 and SIIV or saline and having safety follow-up after vaccination from each vaccine group, the percentage of participants reporting: • Local reactions within 7 days after each vaccination • Systemic events within 7 days after each vaccination • AEs within 1 month after each vaccination • SAEs from the first vaccination up to 1 month after the last vaccination	• Local reactions (redness, swelling, and pain at the injection site) • Systemic events (fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary BNT162b2 Immunogenicity Objective:	**Primary BNT162b2 Immunogenicity Estimand:**	**Primary BNT162b2 Immunogenicity Endpoint:**
To demonstrate that the immune responses elicited by BNT162b2 when coadministered with SIIV (BNT162b2+SIIV) are noninferior to those elicited by BNT162b2 when administered alone	In participants in compliance with the key protocol criteria (evaluable participants): • GMR of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 in the coadministration group to the IgG levels 1 month after vaccination with BNT162b2 in the separate-administration group	• Full-length S-binding IgG levels

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

Objectives	Estimands	Endpoints
Primary SIIV Immunogenicity Objective:	**Primary SIIV Immunogenicity Estimand:**	**Primary SIIV Immunogenicity Endpoints:**
To demonstrate that the immune responses elicited by SIIV when coadministered with BNT162b2 (BNT162b2+SIIV) are noninferior to those elicited by SIIV when administered alone	In evaluable participants: • GMR of the strain-specific HAI (or H3N2-neutralizing antibody) titers 1 month after vaccination with SIIV in the coadministration group to the corresponding HAI (or H3N2-neutralizing antibody) titers in the separate-administration group	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)
Secondary BNT162b2 Immunogenicity Objective:	**Secondary BNT162b2 Estimands:**	**Secondary BNT162b2 Immunogenicity Endpoints:**
To describe the immune responses elicited by BNT162b2 when coadministered with SIIV or administered alone	In evaluable participants from each vaccine group: • GMCs/GMTs at before vaccination and 1 month after vaccination with BNT162b2 • GMFR from before vaccination to 1 month after vaccination with BNT162b2	• Full-length S-binding IgG levels • SARS-CoV-2 neutralizing titers (for a subset of approximately 200 participants)
Secondary SIIV Immunogenicity Objective:	**Secondary SIIV Immunogenicity Estimands:**	**Secondary SIIV Immunogenicity Endpoints:**
To describe the immune responses elicited by SIIV when coadministered with BNT162b2 or administered alone	In evaluable participants from each vaccine group: • GMTs before vaccination and 1 month after vaccination with SIIV • GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination with SIIV	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)

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

Objectives	Estimands	Endpoints
Exploratory Immunogenicity Objective:	**Exploratory Immunogenicity Estimands**	**Exploratory Immunogenicity Endpoints:**
To further describe the immune response elicited by SIIV when coadministered with BNT162b2 or administered alone	In evaluable participants from each vaccine group: • The percentage of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV • The percentage of participants with strain-specific HAI seroconversion 1 month after vaccination with SIIV • The percentage of participants with H3N2 neutralization seroprotection 1 month after vaccination with SIIV • The percentages of participants with H3N2 neutralization seroconversion 1 month after vaccination with SIIV	• Strain-specific HAI titers • H3N2-neutralizing antibody titers (if H3N2-HAI titers cannot be obtained)

2.2. Study Design

This is a Phase 3, multicenter, randomized, 2-arm parallel, observer-blind study in adults 18 through 64 years of age to assess the safety and immunogenicity of a booster dose of BNT162b2 and SIIV given together compared to the vaccines given 1 month apart. Approximately 1126 participants will be randomized at a ratio of 1:1 into the coadministration group and the separate-administration group stratified by age group (18-49 years and 50-64 years) and by history of positive SARS-CoV-2 test by NAAT or rapid antigen test prior to randomization (with and without prior history of SARS-CoV-2). Assuming a 20% nonevaluable rate, there will be approximately 900 evaluable participants. Each participant will participate in the study for approximately 2 months with 3 scheduled visits.

Local reactions (redness, swelling, and pain at the injection site) occurring at the BNT162b2 or saline injection site within 7 days and systemic events (fever, headache, fatigue/tiredness, chills, vomiting, diarrhea, new or worsening muscle pain, and new or worsening joint pain) occurring within 7 days after each vaccination (Visit 1 and Visit 2) will be prompted for and collected daily by the participant in an e-diary device or application. Use of antipyretic/pain medications will also be prompted for and collected daily in the reactogenicity e-diary for 7 days after each vaccination.

AEs and SAEs will be collected from the signing of informed consent through Visit 3 (approximately 1 month after Vaccination 2).

To assess immunogenicity, approximately 30 mL of blood will be collected from all participants at 3 study visits: at Visit 1 (prior to Vaccination 1); at Visit 2 (prior to Vaccination 2); and at Visit 3 (1 month after Visit 2).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

The primary safety endpoints are as follows:

- Local reactions (redness, swelling, and pain at the injection site) within 7 days after each vaccination.
- 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 vaccination.
- AEs within 1 month after each vaccination.
- SAEs from the first vaccination up to 1 month after the last vaccination.

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, within 7 days after each vaccination. This section describes derivations with details for the assessment of local reactions: presence, severity level, duration, and onset day.

Presence or Absence

For each local reaction and any local reaction on any day, Table 3 defines the algorithm to derive the presence of a reaction (yes or no) during the interval within 7 days after each vaccination.

Table 3. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days for Each Vaccination

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

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

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 4.

Table 4. Local Reaction Grading Scale

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[a]
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

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 local reactions will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale.

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

For each local reaction after each vaccination, the maximum severity grade will be derived for the e-diary collection period (within 7 days after each vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination among the severity grades reported for that local reaction in the e-diary.

Duration (First to Last Day Reported)

The duration (days) of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive. Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasts 7 days or less, or the day the reaction ends if it persists beyond the end of the reactogenicity e-diary period following vaccination (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). However, if a reaction is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing event would be the date/day that the next vaccination 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 the reaction with any severity after vaccination.

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

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, fatigue/tiredness, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain within 7 days after each vaccination. The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of event, severity level, duration, and onset day (see Section 3.1.1.1).

The systemic events will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 5.

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

Table 5. System Event Grading Scale

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

Abbreviation: IV = intravenous.

a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 systemic events will be collected on the AE case report form and assessed by the investigator using the AE intensity grading scale.

Oral temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period (7 days after each vaccination) 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.

Temperatures will be measured in degrees Celsius and recorded to 1 decimal place and will be categorized according to the scale shown in Table 6 during analysis.

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

Table 6. Scale for Fever

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

3.1.1.3. Use of Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (7 days after each vaccination). For the use of antipyretic medication within 7 days after each vaccination, 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 (7 days after each vaccination).
- Presence (yes or no) of use of antipyretic medication on any day (within 7 days after each vaccination).
- 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 and including Visit 3. AEs will be categorized according to MedDRA terms. 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. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (refer to Section 5.2.1).

- Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; there is no Tier 1 event identified for BNT162b2 at this stage.

- Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event.

- Tier 3 events are those that are neither Tier 1 nor Tier 2 events.

The primary safety endpoint "AEs within 1 month after each vaccination" and other AE endpoints will be summarized by system organ class and preferred term.

These primary endpoints will be supported by summaries and/or listings of related AEs, severe AEs, immediate AEs (within the first 30 minutes after each vaccination), and AESIs (defined in Section 8.3.8 of the protocol: confirmed myocarditis or pericarditis, confirmed COVID-19 diagnosis or positive SARS-CoV-2 test result by NAAT or rapid antigen test).

3.1.1.5. Serious Adverse Events

SAEs will also be collected from the time of informed consent through and including Visit 3. SAEs will be categorized according to MedDRA terms.

The safety endpoint "SAEs from the first vaccination up to 1 month after the last vaccination" will be summarized by system organ class and preferred term. Additionally, SAEs will be listed.

3.1.2. Primary Immunogenicity Endpoints

- BNT162b2 immunogenicity: Full-length S-binding IgG levels 1 month after vaccination with BNT162b2 (the vaccination is at Visit 1 in the coadministration group and at Visit 2 in the separate-administration group).

- SIIV immunogenicity: Strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) 1 month after vaccination with SIIV (the vaccination is at Visit 1 in the coadministration group and in the separate-administration group).

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

- BNT162b2 immunogenicity:

  a. Full-length S-binding IgG levels from before vaccination to 1 month after vaccination with BNT162b2.

  b. SARS-CoV-2 neutralizing titers (for a subset of approximately 200 participants) from before vaccination to 1 month after vaccination with BNT162b2.

- SIIV immunogenicity: Strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) from before vaccination to 1 month after vaccination with SIIV.

3.3. Other Endpoints

3.3.1. Exploratory Immunogenicity Endpoints

- SIIV immunogenicity: Strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) before vaccination and 1 month after vaccination with SIIV.

3.4. Baseline Variables

Measurements or samples collected prior to the first vaccination are considered the baseline data for the assessments.

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables will be collected including date of birth, sex (male or female), race (Black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, and not reported), racial designation, and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and 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 50th birthday, the participant is considered to be 49 years old.

Medical history will be collected and categorized according to the current version (at the time of reporting) of MedDRA.

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant at Visit 1, a physical examination will be performed and any findings will be recorded in the source documents and, if clinically significant, the findings will be recorded on the medical history CRF.

3.4.2. E-Diary Transmission

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

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 through Visit 3.
- Prohibited medications listed in the 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 the WHO Drug Dictionary.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the Primary Safety Endpoints section (Section 3.1.1).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in the table below. 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 standard operating procedures.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Evaluable BNT162b2 immunogenicity	All eligible randomized participants who receive all vaccinations at Visit 1 as randomized (coadministration group) or receive all vaccinations at Visit 1 and Visit 2 as randomized (separate-administration group), have at least 1 valid and determinate full-length S-binding IgG or SARS-CoV-2 neutralizing titer result from the blood sample collected within the predefined window (within 28-42 days after receipt of BNT162b2) at Visit 2 (coadministration group) or at Visit 3 (separate-administration group), have no reported COVID-19 or new SARS-CoV-2 infection after Visit 1 and through 1 month after BNT162b2 vaccination (Visit 2 for the coadministration group and Visit 3 for the separate-administration group), and have no other important protocol deviations as determined by the clinician.
Evaluable SIIV immunogenicity	All eligible randomized participants who receive all vaccinations at Visit 1 as randomized, have at least 1 valid and determinate HAI titer or H3N2-neutralizing antibody titer result from the blood sample collected within the predefined window at Visit 2 (within 28-42 days after receipt of SIIV), and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who have at least 1 valid and determinate immunogenicity result after receiving study intervention.
Safety	All participants who receive any of the study intervention.

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, 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 medical monitor will identify those participants with important protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

For all the immunogenicity endpoints, the analysis will be based on the relevant evaluable immunogenicity population. An additional analysis may be performed based on the all-available immunogenicity population if there is a ≥10% difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study intervention they actually receive. Missing reactogenicity e-diary data will not be imputed; missing AE start dates will be handled according to the Pfizer safety rules.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for 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 sponsor/Pfizer staff will be blinded to study intervention allocation until the analysis at the completion of the study. All laboratory testing personnel performing serology assays will remain blinded to the study intervention assigned/received throughout the study. Further details can be found in the protocol, Section 6.3. The timing for statistical analysis is specified in Section 7.2.

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypothesis

The primary immunogenicity objective on immune response elicited by BNT162b2 will be evaluated by the following hypothesis (H_{01}):

$$H_{01}: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority, and $\ln(\mu_A)$ and $\ln(\mu_B)$ are the natural log of the geometric mean of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 for the coadministration group and the separate-administration group, respectively. Noninferiority will be declared if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to separate-administration group) is >0.67.

The primary immunogenicity objective on immune response elicited by SIIV will be evaluated by the following hypothesis (H_{02}) for each of the influenza strains:

$$H_{02}: \ln(\mu_C) - \ln(\mu_D) \leq \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for noninferiority, and $\ln(\mu_C)$ and $\ln(\mu_D)$ are the natural log of the geometric mean of the strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) 1 month after vaccination with SIIV for the coadministration group and the separate-administration group, respectively. Noninferiority will be declared for an influenza strain if the lower limit of the 2-sided 95% CI for the GMR (coadministration group to separate-administration group) is >0.67. The primary SIIV immunogenicity objective of the study will be achieved if the noninferiority is met for each of the influenza strains.

5.1.2. Multiplicity Considerations

For the primary immunogenicity assessment of noninferiority of coadministration of BNT162b2 and SIIV to administration of SIIV followed by BNT162b2 1 month later, each of the hypotheses described above in Section 5.1.1 (the hypothesis based on the full-length S-binding IgG levels elicited by BNT162b2 and the hypotheses based on strain-specific HAI titers elicited by the influenza strains in SIIV) will be tested at a 1-sided alpha level of 0.025.

The primary immunogenicity objectives of the study will be achieved if noninferiority of coadministration to separate administration is met for BNT162b2 (full-length S-binding IgG levels) and for each of the influenza strains in SIIV (strain-specific HAI titers). Therefore, the type I error rate for the immunogenicity assessments is well controlled.

5.2. General Methods

Unless stated otherwise, "vaccine group" in this document refers to the coadministration group receiving BNT162b2 and SIIV at the same visit or the separate-administration group receiving SIIV followed by BNT162b2 1 month later.

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% CI where applicable.

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

3-Tier Approach for AE Summary

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.

5.2.2. Analyses for Continuous Endpoints

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

5.2.2.1. Geometric Mean Ratios

Model-Based

As the primary approach (only for primary endpoints), the GMRs and associated 95% CIs will be calculated by exponentiating the difference in LS means of the 2 vaccine groups and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes vaccine group, age group, and corresponding baseline assay results as factors.

Unadjusted

The GMRs will be calculated as the difference in the means of logarithmically transformed assay results between 2 vaccine groups and exponentiating the difference. The associated 2-sided 95% CIs will be obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.2. Geometric Means

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

5.2.2.3. Geometric Mean Fold Rises

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

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

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.3. Methods to Manage Missing Data

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

Missing serology 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimands: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) within 7 days after each vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each vaccination.
- 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 vaccination in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Confirmed e-diary errors will be excluded from the analysis. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.1.2. Supplemental Analyses

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

- Duration (days) of each local reaction after each vaccination.
- Onset day of each local reaction after each vaccination.

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

Figures:

Bar charts with the proportions of participants for each local reaction throughout 7 days after each vaccination will be plotted for each vaccination, by 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

- Estimands: 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 vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each vaccination.
- 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 vaccination in each vaccine group will be presented by maximum severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

6.1.1.2.2. Supplemental Analyses

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

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

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

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

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

Figures:

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

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs within 1 month after each vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 1 month after each vaccination.
- Analysis methodology: Descriptive statistics on a 3-tier approach (Section 5.2.1 and Section 3.1.1.4).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).

- Reporting results: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of AEs within 1 month after each vaccination will be provided for each vaccine group. For both Tier 1 (if any) and Tier 2 events, the between-group difference in proportions and the associated 2-sided 95% CI based on the Miettinen and Nurminen[2] method will be provided for 1 month after vaccination with SIIV and BNT162b2 at Visit 1 for the coadministration group vs 1 month after vaccination with SIIV and saline at Visit 1 for the separate-administration group, and for 1 month after vaccination with SIIV and BNT162b2 at Visit 1 for the coadministration group vs 1 month after vaccination with BNT162b2 at Visit 2 for the separate-administration group. For Tier 1 events (if any), the asymptotic p-values for the difference in proportions will be provided, 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 will be provided for each vaccination in each vaccine group.

6.1.1.3.2. Supplemental Analyses

Related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each vaccination) and AESIs (defined in Section 8.3.8 of the protocol) will also be summarized for each vaccination in each vaccine group.

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

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs from the first vaccination up to 1 month after the last vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: From the first vaccination up to 1 month after the last vaccination.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Intercurrent events and missing data: Missing data will not be imputed except for partial AE start dates (Section 5.3).
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from the first vaccination up to 1 month after the last vaccination will be provided for each vaccination in each vaccine group.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Primary BNT162b2 Immunogenicity

- Full-length S-binding IgG levels 1 month after vaccination with BNT162b2.

6.1.2.1.1. Main Analyses

- Estimands: GMR of full-length S-binding IgG levels 1 month after vaccination with BNT162b2 (at Visit 1) in the coadministration group to the IgG levels 1 month after vaccination with BNT162b2 (at Visit 2) in the separate-administration group (Section 2.1).

- Analysis set: Evaluable BNT162b2 immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: 1 Month after vaccination with BNT162b2.

- Analysis methodology: The GMR and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.1. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 (Section 5.1.1).

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

- Reporting results: The adjusted GMR and 2-sided 95% CI will be calculated based on the primary approach using a linear regression model that includes vaccine group, age group, and baseline (Visit 1 for the coadministration group and Visit 2 for the separate-administration group) full-length S-binding IgG levels as factors. The unadjusted GMR and the associated 2-sided 95% CI will also be provided.

6.1.2.1.2. Supplemental Analyses

Supplemental analysis will be performed in participants without evidence of SARS-CoV-2 infection through 1 month after BNT162b2 vaccination. The unadjusted GMR and the associated 2-sided 95% CI will be provided. The designation of "without evidence of SARS-CoV-2 infection through 1 month after BNT162b2 vaccination" is given to participants who have no serological or virological evidence (prior to the 1-month post–BNT162b2 vaccination blood sample collection) of SARS-CoV-2 infection (ie, N-binding antibody negative before study vaccination and at the 1-month post–BNT162b2 vaccination visit, and no reported SARS-CoV-2 infection or COVID-19 through the 1-month post–BNT162b2 vaccination blood sample collection) and have no medical history of SARS-CoV-2.

6.1.2.2. Primary SIIV Immunogenicity

- Strain-specific HAI titers (or H3N2-neutralizing antibody titers if H3N2-HAI titers cannot be obtained) 1 month after vaccination with SIIV.

6.1.2.2.1. Main Analyses

- Estimands: GMR of the strain-specific HAI (or H3N2-neutralizing antibody) titers 1 month after vaccination with SIIV in the coadministration group to the corresponding HAI (or H3N2-neutralizing antibody) titers in the separate-administration group (Section 2.1).

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

- Analysis time point: 1 Month after vaccination with SIIV.

- Analysis methodology: For each influenza strain, the GMRs and the associated 2-sided 95% CIs will be calculated using the statistical methods described in Section 5.2.2.1. Noninferiority for a strain will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67. The primary SIIV immunogenicity objective of the study will be achieved if the noninferiority is met for each of the influenza strains (Section 5.1.1).

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

- Reporting results: The adjusted GMR and 2-sided 95% CI will be calculated based on the primary approach using a linear regression model that includes vaccine group, age group, and corresponding baseline strain-specific HAI (or H3N2-neutralizing antibody) titers as factors. The unadjusted GMR and the associated 2-sided 95% CI will also be provided.

6.2. Secondary Endpoints

6.2.1. Secondary BNT162b2 Immunogenicity Endpoints

6.2.1.1. Full-Length S-Binding IgG Levels

6.2.1.1.1. Main Analysis

- Estimands:

  a. GMCs of full-length S-binding IgG levels before vaccination and 1 month after vaccination with BNT162b2 (Section 2.1).

b. GMFRs of full-length S-binding IgG levels and SARS-CoV-2 neutralizing titers from before vaccination to 1 month after vaccination with BNT162b2 (Section 2.1).

- Analysis set: Evaluable BNT162b2 immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).

- Analysis time point: Before vaccination (Visit 1 for the coadministration group and Visit 2 for the separate-administration group) and 1 month after vaccination with BNT162b2.

- Analysis methodology: The GMCs and the associated 2-sided 95% CIs at before vaccination and 1 month after vaccination with BNT162b2 will be provided for each vaccine group using the statistical methods described in Section 5.2.2.2. The GMFRs and the associated 2-sided 95% CIs from before vaccination to 1 month after vaccination with BNT162b2 will be provided for each vaccine group using the statistical methods described in Section 5.2.2.3.

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

- Reporting results: GMCs and the associated 2-sided 95% CIs will be provided for each vaccine group at before vaccination and 1 month after vaccination with BNT162b2. GMFRs from before vaccination to 1 month after vaccination with BNT162b2 and the associated 2-sided 95% CIs will be provided for each vaccine group.

6.2.1.2. SARS-CoV-2 Neutralizing Titers (for a Subset of Approximately 200 Participants)

6.2.1.2.1. Main Analysis

Analyses for SARS-CoV-2 neutralizing titers are similar to those for full-length S-binding IgG levels described in Section 6.2.1.1.1.

6.2.2. Secondary SIIV Immunogenicity Endpoint – Strain-Specific HAI (or H3N2-Neutralizing Antibody) Titers

6.2.2.1. Main Analysis

- Estimands:

  a. GMTs of the strain-specific HAI (or H3N2-neutralizing antibody) titers before vaccination and 1 month after vaccination with SIIV (Section 2.1).

  b. GMFRs of the strain-specific HAI (or H3N2-neutralizing antibody) titers from before vaccination to 1 month after vaccination with SIIV (Section 2.1).

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

- Analysis time point: Before vaccination (at Visit 1) and 1 month after vaccination with SIIV.

- Analysis methodology: The GMTs and the associated 2-sided 95% CIs at before vaccination and 1 month after vaccination with SIIV will be provided for each vaccine group using the statistical methods described in Section 5.2.2.2. The GMFRs and the associated 2-sided 95% CIs from before vaccination to 1 month after vaccination with SIIV will be provided for each vaccine group using the statistical methods described in Section 5.2.2.3.

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

- Reporting results: GMTs and the associated 2-sided 95% CIs will be provided for each vaccine group at before vaccination and 1 month after vaccination with SIIV. GMFRs from before vaccination to 1 month after vaccination with SIIV and the associated 2-sided 95% CIs will be provided for each vaccine group.

6.3. Other Endpoints

6.3.1. Exploratory Endpoints

6.3.1.1. Strain-Specific HAI Titers ≥1:40 1 Month After Vaccination With SIIV

6.3.1.1.1. Main Analysis

- Estimand: Percentage of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV (Section 2.1).

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

- Analysis time point: 1 Month after vaccination with SIIV.

- Analysis methodology: For each influenza strain, counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of participants with strain-specific HAI titers ≥1:40 1 month after vaccination with SIIV will be provided for each vaccine group using the statistical methods described in Section 5.2.1.

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

- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

6.3.1.2. Strain-Specific HAI Seroconversion 1 Month After Vaccination With SIIV

6.3.1.2.1. Main Analysis

- Estimand: Percentage of participants with strain-specific HAI seroconversion 1 month after vaccination with SIIV (Section 2.1).

  HAI seroconversion is defined as:

  a. an HAI titer <1:10 before SIIV vaccination and an HAI titer ≥1:40 1 month after SIIV vaccination or

  b. an HAI titer ≥1:10 before vaccination and a minimum 4-fold rise in HAI titer 1 month after SIIV vaccination.

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

- Analysis time point: 1 Month after vaccination with SIIV.

- Analysis methodology: For each influenza strain, counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of participants with strain-specific HAI titer seroconversion 1 month after vaccination with SIIV will be provided for each vaccine group using the statistical methods described in Section 5.2.1.

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

- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

6.3.1.3. H3N2 Neutralization Seroprotection/Seroconversion

6.3.1.3.1. Main Analysis

- Estimands:

  - Percentage of participants with H3N2 neutralization seroprotection 1 month after vaccination with SIIV.

  - Percentage of participants with H3N2 neutralization seroconversion 1 month after vaccination with SIIV.

Seroprotection for H3N2-neutralizing titers is defined as a neutralizing titer ≥1:80.

Seroconversion for H3N2-neutralizing titers is defined based on prevaccination neutralizing titer:

a. When prevaccination neutralizing titer is <1:20, seroconversion is achieved if the postvaccination neutralizing titer is ≥1:80.

b. When prevaccination neutralizing titer is ≥1:20, seroconversion is achieved if the fold rise from the prevaccination neutralizing titer to the postvaccination neutralizing titer is ≥4.

- Analysis set: Evaluable SIIV immunogenicity population, all-available immunogenicity population (as applicable) (Section 4).
- Analysis time point: 1 Month after vaccination with SIIV.
- Analysis methodology: Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs of participants with H3N2 neutralization seroprotection and seroconversion 1 month after vaccination with SIIV will be provided for each vaccine group using the statistical methods described in Section 5.2.1.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: Counts, percentages, and the associated Clopper-Pearson 95% CIs will be provided for each vaccine group.

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6.4. Subset Analyses

Subgroup analyses based on age group, sex, race (if appropriate), and racial designation, as well as baseline SARS-CoV-2 status (based on N-binding antibody results at Visit 1 before vaccination and medical history of SARS-CoV-2), will be performed on all primary safety and immunogenicity 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 at vaccination, age group, sex, race, racial designation, ethnicity, and baseline SARS-CoV-2 infection status (based on N-binding antibody results at Visit 1 before vaccination and medical history of SARS-CoV-2), as well as timing of the third dose of BNT162b2 prior to BNT162b2 vaccination received during the study, will be summarized using descriptive statistics for each vaccine group based on the safety population and the evaluable BNT162b2/SIIV immunogenicity population.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of participants with at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group for the safety population.

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 disposition summary. In addition, the numbers and percentages of participants who receive vaccinations (Vaccination 1 at Visit 1 and Vaccination 2 at Visit 2), who complete the study, and who withdraw from the study (including withdrawals before each planned vaccination 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.

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 (before Vaccination 1, 1 month after Vaccination 1 but before Vaccination 2, and 1 month after Vaccination 2).

6.5.2.3. Transmission of E-Diaries

The number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period for each vaccination will be summarized according to the vaccine actually received.

The safety population will be used.

6.5.3. Study Intervention Exposure

6.5.3.1. Vaccination Timing and Administration

For each vaccination, 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 percentage calculations is the total number of randomized participants in the given vaccine group or overall, per age group.

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

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

6.5.4. Prior/Concomitant Vaccinations and Concomitant Medications

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

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs are described in the Primary Safety Endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis is planned for this study. A program-wide DMC will monitor the safety data for this study.

7.2. Analysis Timings

Statistical analyses will be performed when the study is completed and the database is locked.

8. REFERENCES

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

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic Therapeutic Chemical
BLQ	below the limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
ICD	informed consent document
IgG	immunoglobulin G
IRT	interactive response technology
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
RCDC	reverse cumulative distribution curve
S	spike protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIIV	seasonal inactivated influenza vaccine
WHO	World Health Organization

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Signed By:	Date(GMT)	Signing Capacity
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