Protocol C5261001 – Substudy A

A PHASE 1 RANDOMIZED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED MODIFIED RNA VACCINE CANDIDATES AGAINST COVID-19 AND INFLUENZA IN HEALTHY INDIVIDUALS – SUBSTUDY A

Statistical Analysis Plan (SAP)

Version: 2

Date: 19 Jan 2023

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APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 03 Nov 2022	1 18 Oct 2022	N/A	N/A
2 19 Jan 2023	2 09 Dec 2022	Update to match protocol amendment 2	• Updated throughout to reflect the addition of a new age stratum and the removal of 22/23 specific HAI strains • Updated Table 3 and Table 4 to reflect that redness/swelling <2 cm is not considered a reaction • Updated Section 4 to specify how participants enrolled at multiple sites will be handled in the outputs • Updated Section 6.3.2 with more details about the C4591044 data • Updated Section 6.4 with details about subgroup analyses by SARS-CoV-2 status at baseline

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C5261001 – Substudy A.

2.1. Modifications to the Analysis Plan Described in the Protocol

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

2.2. Study Objectives, Endpoints, and Estimands

The primary, secondary, and tertiary/exploratory objectives, associated endpoints, and associated estimands are described in the following table.

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Objectives	Estimands	Endpoints
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To describe the safety and tolerability of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age separately and combined, receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs from the first vaccination through 4 weeks after vaccination • SAEs from the first vaccination through 6 months after vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	The percentage of participants 18 through 64 years of age and ≥65 years of age separately and combined with: • Abnormal troponin I laboratory values 2 days and 1 week after vaccination	Troponin I laboratory parameters detailed in Section 10.2 of the protocol
	The percentage of participants 18 through 64 years of age and ≥65 years of age separately and combined with: • New ECG abnormalities 2 days and 1 week after vaccination	ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 10.9.8.4.1 of the protocol
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at various dose-level combinations in participants ≥18 years of age	In participants 18 through 64 years of age and ≥65 years of age separately, complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 1, 4, and 8 weeks after vaccination • GMFR from before vaccination to 1, 4, and 8 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 1, 4, and 8 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at 1, 4, and 8 weeks after vaccination • The percentage of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after vaccination • The percentage of participants with HAI titers ≥1:40 for all strains at 1, 4, and 8 weeks after vaccination	HAI titers for the seasonal strains (CCI) recommended by WHO for recombinant or cell-based influenza vaccines

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	In participants 18 through 64 years of age and ≥65 years of age separately, having received qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5), complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at 1, 4, and 8 weeks after vaccination for each strain • GMFR from before vaccination to 1, 4, and 8 weeks after vaccination for each strain • Percentages of participants with seroresponse[b] at 1, 4, and 8 weeks after vaccination for each strain	• SARS-CoV-2 Omicron BA.4/BA.5-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the immune response to emerging VOCs in participants ≥18 years of age		SARS-CoV-2–neutralizing titers for VOCs not already specified

a. Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest, or an HAI titer of ≥1:10 prior to vaccination with a 4-fold rise at the time point of interest.

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

2.2.1. Primary Estimands

The primary estimands for the primary safety objective will use the treatment policy strategy and estimate the safety rate (reactogenicity, AEs and SAEs, troponin I values, and ECGs) regardless of whether an intercurrent event occurs.

- The reactogenicity estimands (local reactions and systemic events) have the following 5 attributes:
  - **Population:** Participants 18 through 64 years of age and ≥65 years of age who have received at least 1 dose of study intervention.
  - **Variables:** Each prompted item from the e-diary from Days 1 through 7 following vaccinations.
  - **Treatment condition:** [redacted]µg qIRV/[redacted]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [redacted]µg qIRV [redacted]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [redacted]µg qIRV/[redacted]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [redacted]µg qIRV, [redacted]µg qIRV, or [redacted]µg bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV, administered on Day 1.

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- **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation from the study, etc.), if collected, will be included.

- **Population-level summary:** The rates of reporting each prompted reactogenicity item will be estimated by study intervention for participants 18 through 64 years of age and ≥65 years of age separately and combined.

- The AE and SAE estimands have the following 5 attributes:

  - **Population:** Participants 18 through 64 years of age and ≥65 years of age who have received at least 1 dose of study intervention.

  - **Variables:**

    - AEs reported through 4 weeks after vaccination.

    - SAEs reported through 6 months after vaccination.

  - **Treatment condition:** [CCI] µg qIRV/[CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV [CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV [CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV, [CCI] µg qIRV, or [CCI] µg bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV, administered on Day 1.

  - **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation from the study, etc.), if collected, will be included.

  - **Population-level summary:** The rates of reporting AEs and SAEs for each study intervention for participants 18 through 64 years of age and ≥65 years of age separately and combined.

- The troponin I estimand has the following 5 attributes:

  - **Population:** Participants 18 through 64 years of age and ≥65 years of age who have received at least 1 dose of study intervention.

  - **Variables:** Presence of abnormal troponin I values 2 days and 1 week after vaccination.

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- **Treatment condition:** [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI]µg qIRV [CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI]µg qIRV, [CCI]µg qIRV, or [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV, administered on Day 1.

- **Intercurrent events:** All data after an intercurrent event (use of rescue medication, missing e-diary entries on certain days, discontinuation from the study, etc.), if collected, will be included.

- **Population-level summary:** The percentage of participants reporting abnormal troponin I values 2 days and 1 week after vaccination for each study intervention for participants 18 through 64 years of age and ≥65 years of age separately and combined.

- The ECG estimand has the following 5 attributes:

  - **Population:** Participants 18 through 64 years of age and ≥65 years of age who have received at least 1 dose of study intervention.

  - **Variables:** Presence of new ECG abnormalities (consistent with probable or possible myocarditis or pericarditis) 2 and 7 days after vaccination.

  - **Treatment condition:** [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI]µg qIRV, [CCI]µg qIRV, or [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV, administered on Day 1.

  - **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation from the study, etc.), if collected, will be included.

  - **Population-level summary:** The percentage of participants reporting new ECG abnormalities 2 and 7 days after vaccination for each study intervention for participants 18 through 64 years of age and ≥65 years of age separately and combined.

*Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in the protocol as the reference strain.

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2.2.2. Secondary Estimands

The secondary estimands for the secondary objective (immunogenicity) will use the hypothetical strategy and estimate the vaccine immune response when an intercurrent event does not occur. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed. It includes the following 5 attributes:

- **Population:** Participants 18 through 64 years of age and ≥65 years of age, as defined by the inclusion and exclusion criteria.
- **Variables:**
  - HAI titers for each strain, by study intervention group with qIRV, at each time point.
  - HAI titer fold rise for each strain, by study intervention group with qIRV, from before vaccination to each time point after vaccination.
  - Presence of HAI seroconversion for each strain, by study intervention group with qIRV, at each time point after vaccination.
  - Presence of HAI titers ≥1:40 for each strain, by study intervention group with qIRV, before vaccination and at each time point after vaccination.
  - Presence of HAI seroconversion for all strains, by study intervention group with qIRV, at each time point after vaccination.
  - Presence of HAI titers ≥1:40 for all strains, by study intervention group with qIRV, before vaccination and at each time point after vaccination.
  - SARS-CoV-2–neutralizing titer for each strain, by study intervention group with a BNT162b2 dose.
  - SARS-CoV-2–neutralizing titer fold rise for each strain, by study intervention group with a BNT162b2 dose, from before vaccination to each time point after vaccination.
  - Presence of seroresponse for each strain-specific neutralizing titer, by study intervention group with a BNT162b2 dose.
- **Treatment condition:** [CCI] µg qIRV/[CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV [CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV/[CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV, [CCI] µg qIRV, or [CCI] µg bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV, administered on Day 1.

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- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:
  - Not receiving the vaccine as randomized.
  - Not meeting the study inclusion/exclusion criteria.
  - Having major protocol deviations (received prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).
  - Undergoing blood collection outside of the defined window (26 to 35 days, inclusive, after vaccination).

  All data after intercurrent events, if collected, will be excluded.
- Population-level summary:
  - HAI GMTs at each time point and GMFRs from before vaccination to each time point after vaccination, and the proportion of participants achieving HAI seroconversion at each time point and the proportion of participants with HAI titers ≥1:40 before vaccination and at each time point after vaccination, will be estimated for each strain, by study intervention group with qIRV, for participants 18 through 64 years of age and ≥65 years of age separately.
  - SARS-CoV-2 GMT at each time point and GMFRs from before vaccination to each time point after vaccination, and the proportion of participants with seroresponse at 1, 4, and 8 weeks after vaccination, will be estimated for each strain by study intervention group with a BNT162b2 dose, for participants 18 through 64 years of age and ≥65 years of age separately.

*Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in the protocol as the reference strain.

2.2.3. Additional Estimands

The additional estimands for the tertiary/exploratory objective will use the hypothetical strategy. It includes the following 5 attributes:

- **Population:** Participants 18 through 64 years of age and ≥65 years of age, as defined by the inclusion and exclusion criteria.
- **Variables:**
  - SARS-CoV-2 VOC–neutralizing titer for VOCs not already specified, by study intervention group with a BNT162b2 dose.

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- SARS-CoV-2 VOC–neutralizing titer fold rise for VOCs not already specified, by study intervention group with a BNT162b2 dose, from before vaccination to each time point after vaccination.
- Presence of seroresponse for VOCs not already specified, by study intervention group with a BNT162b2 dose.

- **Treatment condition:** [CCI] µg qIRV/[CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV/[CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), [CCI] µg qIRV [CCI] µg bivalent BNT162b2 (original*/Omi BA.4/BA.5), or [CCI] µg bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV, administered on Day 1.
- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:
  - Not receiving the vaccine as randomized.
  - Not meeting the study inclusion/exclusion criteria.
  - Having major protocol deviations (received prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).
  - Undergoing blood collection outside of the defined window (26 to 35 days, inclusive, after vaccination).

  All data after the above intercurrent events, if collected, will be excluded.
- **Population-level summary:** GMTs and GMFRs of SARS-CoV-2 VOC–neutralizing titers for VOCs not already specified, and associated 2-sided 95% CIs, will be estimated by study intervention group with a BNT162b2 dose for participants 18 through 64 years of age and ≥65 years of age separately.

*Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in the protocol as the reference strain.

2.3. Study Design

This is a Phase 1 randomized, open-label substudy to describe the safety and immunogenicity of up to 3 dose-level combinations of qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5). Approximately 360 participants will be enrolled across 2 age strata: approximately 180 participants 18 through 64 years of age and approximately 180 participants ≥65 years of age. The participants will be randomized equally (30 participants per group) to receive a dose of either:

- qIRV/bivalent BNT162b2 (original*/Omi BA.4/BA.5), at 1 of the 3 dose-level combinations shown in Table 2.

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- CCI µg qIRV,
- CCI µg qIRV, or
- CCI µg Bivalent BNT162b2 (original/Omi BA.4/BA.5) administered concurrently in the opposite arm to licensed QIV.

*Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in the protocol as the reference strain.

Table 2. Study Interventions and qIRV/Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combinations

Group Number	Dose-Level Combination	qIRV Dose	Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose	Total modRNA Dose
1	1	CCI µg, ie, CCI	CCI µg, ie, • CCI µg of original BNT162b2 and • CCI µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	CCI µg
2	2	CCI µg, ie, CCI	CCI µg, ie, • CCI µg of original BNT162b2 and • CCI µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	µg
3	3	CCI µg, ie, CCI	CCI µg, ie, • CCI µg of original BNT162b2 and • CCI µg of BNT162b2 Omicron (B.1.1.529 sublineage BA.4/BA.5)	µg
4	N/A	CCI µg, ie, CCI	N/A	µg
5	N/A	CCI µg, ie, CCI	N/A	µg
6	N/A	N/A	CCI µg of bivalent BNT162b2 (original/Omi BA.4/BA.5), administered concurrently in the opposite arm to licensed QIV	µg

As determined based on emergent data from ongoing clinical studies with BNT162b2, dose-level combinations 1 and/or 3 may be omitted from this study. Safety and immunogenicity data from studies previously conducted in participants of a similar age range having received 1 dose of BNT162b2 at a dose level of CCI µg or CCI µg may be used as a control during analysis.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Local reactions through 7 days following vaccination.
- Systemic events through 7 days following vaccination.
- AEs through 4 weeks after vaccination.
- SAEs through 6 months after vaccination.
- Abnormal troponin I laboratory values 2 days and 1 week after vaccination.
- New ECG abnormalities 2 days and 7 days after vaccination.

3.1.1. Local Reactions

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

Presence or Absence

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

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

For each local reaction and any local reaction on any day, Table 3. explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of vaccination.

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

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of each local reaction.	The reaction is reported as "yes" with a diameter of >2.0 cm for redness/swelling or "yes" for pain any day from Day 1 through Day 7.	The reaction is reported as "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on all 7 days or as a combination of "no" and missing on all 7 days.	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.

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

Table 4. Derived Variables for Presence of Any Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of any local reaction.	The reaction is reported as "yes" with a diameter of >2.0 cm for redness/swelling or "yes" for pain any day from Day 1 through Day 7.	For all 3 local reactions, participant reports "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on all 7 days (Day 1 through Day 7) or as a combination of "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) and missing on all 7 days. (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

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

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, severe, or potentially life-threatening based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

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Table 5. Local Reaction Grading Scale

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

For each local reaction, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each vaccination) as follows:

maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration of Each Local Reaction (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 4), the maximum duration (resolution date of reaction - start date of reaction + 1) will be derived .

Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to "missing." Participants with no reported reactions have no duration.

Onset Day of Each Local Reaction

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

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

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3.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain, from Day 1 through Day 7, where Day 1 is the day of vaccination.

The derivations for systemic events will be handled in a way similar to the way local reactions are handled for presence of event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.1).

1. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7).
2. Maximum severity of each systemic event on any day (Day 1 through Day 7).
3. Duration of each systemic event.
4. Onset day of each systemic event.
5. Presence (yes or no) of each severe systemic event on each and any of the 7 days.

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

Table 6. Systemic Event Grading Scale

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

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Table 6. Systemic Event Grading Scale

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

Oral temperature will be collected in the evening, daily, for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of 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.

Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting.

Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 7 for summary of maximum temperature. Fever will be grouped into ranges for the analysis according to Table 7.

Table 7. Scale for Fever

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

Note: Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F).

Temperatures <35.0°C and >42.0°C will be excluded from the analysis. If a participant reports a fever (or severity of fever) by accident, the correct temperature will be transcribed in a data handling memo to be included in the analysis, and the temperature that is confirmed as incorrect will not be included in the analysis.

3.1.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of vaccination. For the use of antipyretic medication from Day 1 through Day 7 after vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1), where applicable.

- Presence (yes or no) of use of antipyretic medication on each day (Day 1 through Day 7).
- Presence (yes or no) of use of antipyretic medication on any day (Day 1 through Day 7).

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- 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.

3.1.4. Adverse Events

Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer Vaccine data standard rules. AEs will be collected from informed consent signing through 4 weeks following vaccination (Visit 4).

The following derivations will be included for each participant:

- Any AE reported.
- Any related AE reported.
- Any immediate AE (acute reactions were assessed for at least 30 minutes after study intervention administration).
- Any severe AE.
- Any life-threatening AE.
- Any AE leading to study withdrawal.
- Any AE leading to death.
- Any AESI.
    - A confirmed diagnosis of influenza.
    - A confirmed diagnosis of myocarditis or pericarditis occurring within 4 weeks after vaccination.
    - Confirmed COVID-19 diagnosis through the end of the study (clinical signs/symptoms and positive SARS-CoV-2 NAAT or rapid antigen test result).

3.1.5. Serious Adverse Events

SAEs will be collected from the time the participant provides informed consent through approximately 6 months after vaccination (Visit 6).

3.1.6. Laboratory Data

- Abnormal troponin I laboratory values 2 days and 1 week after vaccination.

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

Hematology	Chemistry
N/A	Cardiac troponin I

Clinically significant abnormal laboratory findings should be recorded in the AE CRF. Additionally, the primary criterion for abnormality will follow the Pfizer safety rule book.

3.1.7. Electrocardiograms

An ECG abnormality is defined as any new abnormality that, as judged by a cardiologist, is consistent with probable or possible myocarditis or pericarditis, including:

- Sustained atrial or ventricular arrhythmias.
- Second-degree Mobitz type II or worse AV block or new bundle branch block.
- Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis.

ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs and should be evaluated further, as clinically warranted.

3.2. Secondary Endpoints

- HAI titers for each strain, by study intervention group with qIRV.
- HAI titer fold rise for each strain, by study intervention group with qIRV.
- Presence of HAI seroconversion for each strain, by study intervention group with qIRV.
- Presence of HAI titers ≥1:40 for each strain, by study intervention group with qIRV.
- Presence of HAI seroconversion for all strains, by study intervention group with qIRV.
- Presence of HAI titers ≥1:40 for all strains, by study intervention group with qIRV.
- SARS-CoV-2–neutralizing titer for each strain, by study intervention group with a BNT162b2 dose.

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- SARS-CoV-2–neutralizing titer fold rise for each strain, by study intervention group with a BNT162b2 dose.

- Presence of seroresponse for each strain-specific neutralizing titer, by study intervention group with a BNT162b2 dose.

3.3. Other Endpoints

- SARS-CoV-2 VOC–neutralizing titer for VOCs not already specified, by study intervention group with a BNT162b2 dose.

- SARS-CoV-2 VOC–neutralizing titer fold rise for VOCs not already specified, by study intervention group with a BNT162b2 dose.

- Presence of seroresponse for VOCs not already specified, by study intervention group with a BNT162b2 dose.

3.4. Baseline Variables

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

3.4.1. Demographics and Medical History

The demographic variables are age at vaccination (in years), sex (male or female), race (Black/African American, American Indian, or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, not reported), ethnicity (Hispanic/Latino/of Spanish origin, non-Hispanic/non-Latino, not reported), and racial designation (Japanese, other). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis. BMI will also be included in the demographic variables.

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

3.4.2. E-Diary Completion

An e-diary will be considered transmitted if any data for the 3 local reactions (redness, swelling, and pain at the injection site), 7 systemic events (vomiting, diarrhea, headache, fatigue, chills, new or worsening muscle pain, and new or worsening joint pain) and fever, or use of antipyretic/pain medication to treat symptoms are present on any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted.

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An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

For transmitted e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," and "Day 7".

For completed e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "Day 7," and "Day 1 through Day 7".

"Day 1 through Day 7" is the variable for participants who completed e-diaries on all 7 days.

For e-diaries that are incomplete, an indicator variable for the percentage of days without data will be derived as follows:

= 1, if data have been transmitted and are complete for 7 days (100%)

= 2, if data have been transmitted and are complete for 6 days (≥75% to <100%)

= 3, if data have been transmitted and are complete for 4 or 5 days (≥50% to <75%)

= 4, if data have been transmitted and are complete for 2 or 3 days (≥25% to <50%)

= 5, if data have been transmitted and are complete for 0 or 1 day (≥0% to <25%)

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

The name and date of administration for any concomitant medications and nonstudy vaccinations received from 28 days prior to study enrollment until the last visit (Visit 6) will be collected and recorded in the CRF.

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

- Prior receipt of any COVID-19 vaccine.
- Prior receipt of any pneumococcal vaccine.
- Licensed influenza vaccine, if received during the prior calendar year.
- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 6).
- Prohibited medications listed in Section 10.9.6.7.1 of the protocol, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

Nonstudy vaccines and concomitant medications will be coded using the WHODD.

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3.5. Safety Endpoints

Local reaction, systemic event, AE, and SAE assessments and assessments of ECG abnormalities and abnormal troponin I laboratory values are described above in the primary safety endpoints.

3.5.1. Adverse Events

As this is a Phase 1 study, with limited sample size included in each study intervention group, the value of applying the 3-tier approach is limited. Therefore, safety assessment may be best carried out using descriptive statistics only.

3.5.2. Physical Examinations, Including Vital Signs

A physical examination will be performed at the screening visit and, if clinically indicated, prior to the participant's first vaccination.

Physical examination findings collected during the study will be considered source data and will not be required to be reported. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

The participant's oral temperature, pulse rate, and seated blood pressure will be measured at screening, prior to vaccination at Visit 1, at Visit 2, and at Visit 3. Weight and height will also be measured at screening. Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

3.5.3. Laboratory Data

The clinical safety laboratory assessments (troponin I) are 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 standard operating procedures.

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All participants who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame (26-35 days after vaccination), have at least 1 valid and determinate assay result at the 4-week postvaccination visit, and have no major protocol violations.

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Population	Description
mITT	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.
Safety	All participants who receive the study intervention.

Major protocol deviations will be determined by clinical review. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity or efficacy, eg, participant receipt of a prohibited vaccine or medication/treatment 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 protocol deviations before any analysis is carried out.

The APE field will be included in the PIPD form from the CORD system and is used to help identify protocol deviations that may exclude participants from a particular population. For each reporting event, the most current endorsed version of the PIPD list must be used to generate the protocol deviation data set for analysis and reporting.

The APE flags for this study are as follows:

YES-POP1 (participants excluded from the safety population)
YES-POP2 (participants excluded from the evaluable immunogenicity population)
YES-POP4 (participants identified as having multiple enrollments at different sites)

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

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population.

An additional analysis may be performed based on the mITT population if there is a large enough difference (>10%) in sample size between the mITT population and the evaluable immunogenicity population. Participants will be summarized according to the study intervention group to which they were randomized.

Vaccinated but not randomized: These participants will be included in the safety population for safety analysis and will be reported under the study intervention based on the vaccine received but will be excluded from immunogenicity analyses.

Randomized but not vaccinated: These participants will be included in the randomized population but will be excluded from safety analyses.

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Randomized but received incorrect vaccine: These participants will be excluded from the evaluable population for immunogenicity but will be included in the mITT population for immunogenicity analyses if data are available and will be reported under the study intervention based on the randomized vaccine. These participants will also be included in the safety population for safety analysis and will be reported under the study intervention based on the vaccine received.

For participants enrolling at multiple sites: Any participants enrolling at more than 1 site in the study will be removed from all populations. These participants will be followed for safety and reported separately from the other participants.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no hypotheses and decision rules defined for the study. A descriptive estimation approach will be used to assess all study objectives in the study.

Point estimates and nominal 95% CIs will be provided for all safety and immunogenicity endpoints at each planned analysis.

No formal multiplicity adjustments will be applied due to multiple endpoints or multiple looks for the same endpoint.

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 binary variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson)[1] and implemented in SAS PROC FREQ.

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

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

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5.2.2.2. Geometric Mean Fold Rises

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

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the line first going down and then to the right to the next assay value.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for handling missing AE dates, missing AE severity, missing laboratory test values, and missing ECG values will be applied according to the Pfizer safety rules. Missing data handling rules on the safety data are described in detail in the corresponding endpoint sections.

5.3.1.1. Reactogenicity Data

Completely missing reactogenicity e-diary data will not be imputed.

For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Day 1 through 7)" data will be considered nonmissing.

The reactogenicity data are collected through the reactogenicity e-diary, which does not allow participants to skip the question. Therefore, for a specific day, if the e-diary data are transferred for that day, all the reactogenicity data for the participant on that day are nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.1.1 and Section 3.1.2.

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In summary, for any participant with all 7 days of the e-diary missing, this will not be included in the analysis (ie, assuming MCAR). If only 1 to 6 days of e-diary data are transferred, the reactogenicity data for the missing day(s) are considered as answering "no" for all reactions. This is based on the common assumption that no reports mean no events.

5.3.2. Immunogenicity Data

Any assay results above the LLOQ are considered accurate, and their quantitated values will be reported. Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

When calculating a fold rise, the assay results will be converted to 0.5 × LLOQ if assay results are < LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

Values for sera that are insufficient (QNS), indeterminate results or values recorded as "not done" will be set to "missing." Additionally, any time point with no blood draws will not be included in the analysis. No imputation will be done for these missing values, as MCAR is assumed for immunogenicity data.

LLOQ results for each assay used in this study will be included in serology data transfer once they are available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Local Reactions and Systemic Events

6.1.1.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting each event, using the Clopper-Pearson method (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 vaccination; for participants who discontinue, all collected data will be included; intermediate missing values will not be imputed. Partially missing e-diary data are imputed as "no" (Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.

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- Analysis timing: Day 1 through Day 7 after vaccination.
- Reporting results:
  - Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented for each study intervention group and overall, for participants 18 through 64 years of age and ≥65 years of age separately and combined.
  - Bar charts with the proportions of participants for each and any local reaction, and each and any systemic event, through the 7 days following vaccination will be plotted for each study intervention group and overall. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

6.1.1.2. Sensitivity/Supplementary Analyses

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.1 and Section 3.1.2, will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction and each systemic event after vaccination.
- Onset day of each local reaction and each systemic event after vaccination.
- Presence of each and any severe local reaction and each and any severe systemic event, on each of the 7 days and for "any day (Day 1 through Day 7)."

The presentation of the results will include a basic descriptive summary without 95% CIs (Section 5.2.1).

These continuous endpoints will be summarized by displaying the n, mean, median, standard deviation, minimum, and maximum for each study intervention group and overall, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

In addition, the proportions of participants reporting prompted local reactions and systemic events, by maximum severity level, with any e-diary errors will be included as a supplemental summary for participants 18 through 64 years of age and ≥65 years of age separately and combined.

6.1.2. AEs and SAEs

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).

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- Analysis methodology: 95% CI of the proportion of participants reporting those events, using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: Day 1 through 4 weeks after vaccination for AEs; Day 1 through 6 months after vaccination for SAEs.
- Intercurrent events and missing data: All data collected are included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Reporting results:
  - The number of participants with AEs though 4 weeks after vaccination (n), proportion (%), and associated 2-sided Clopper-Pearson 95% CI will be presented for each study intervention group and overall, for participants 18 through 64 years of age and ≥65 years of age separately and combined.
  - The number of participants with SAEs though 6 months after vaccination (n), proportion (%), and associated 2-sided Clopper-Pearson 95% CI will be presented for each study intervention group and overall, for participants 18 through 64 years of age and ≥65 years of age separately and combined.
  - Descriptive statistics, including the proportion (%), the numerator (n) and the denominator used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented for each SOC and each PT within each SOC for each study intervention group and overall, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

6.1.2.2. Sensitivity/Supplementary Analysis

To support the assessment of AEs, the endpoints below as specified in Section 3.1.4 and Section 3.1.5 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs
- Related AEs
- Severe AEs
- Life-threatening AEs
- AEs leading to study withdrawal
- AEs leading to death
- AESIs

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

In addition, any AEs occurring up to 48 hours after blood draws at Visit 4 and Visit 5 will be listed.

6.1.3. Laboratory Parameters

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).
- Analysis timing: Within 2 to 4 and within 6 to 8 days after vaccination.
- Intercurrent events and missing data: All data collected are included. Missing dates/laboratory values will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Reporting results: The number of participants with abnormal troponin I laboratory values within the visit window at Visits 2 and 3 after vaccination (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented by study intervention group, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

6.1.4. Electrocardiograms

6.1.4.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis timing: Up to Visits 2 and 3 after vaccination.
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).
- Supporting objective: Primary safety objective.
- Intercurrent events and missing data: All data collected are included. Missing ECG values will be handled according to Pfizer safety rules.
- Reporting results: The number of participants with new ECG abnormalities up to Visits 2 and 3 after vaccination (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented for each study intervention group, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

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6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis methodology: Descriptive summary statistics (Section 5.2.2).
- Analysis timing: 1, 4, and 8 Weeks after study intervention administration.
- Intercurrent events and missing data: All data collected after or at intercurrent events will be excluded. Antibody titers below the LLOQ will be treated as specified in Section 5.3.2. Missing data will not be imputed.
- Reporting results:
    - The SARS-CoV-2 GMT at each time point and GMFRs from before vaccination to each time point after vaccination, and the proportion of participants with seroresponse at 1, 4, and 8 weeks after vaccination, will be estimated for each strain, by study intervention group with a BNT162b2 dose, and separately by age group.
    - Descriptive statistics, including the sample size (n), GMTs, GMFRs, and 95% CI for the GMTs and GMFRs, will be presented for each strain by study intervention group with qIRV (Section 5.2.2), for participants 18 through 64 years of age and ≥65 years of age separately.
    - The proportion of participants achieving HAI seroconversion and the associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain by study intervention group with qIRV, for participants 18 through 64 years of age and ≥65 years of age separately.
    - The proportion of participants with HAI titers ≥1:40 before vaccination and at each time point after vaccination and the associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain by study intervention group with qIRV, for participants 18 through 64 years of age and ≥65 years of age separately.
    - HAI GMTs for each strain and the associated 95% CIs will be plotted by study intervention group with qIRV, for participants 18 through 64 years of age and ≥65 years of age separately.
    - HAI seroconversion rate for each strain, along with the associated 95% CIs, will be presented by study intervention group with qIRV, for participants 18 through 64 years of age and ≥65 years of age separately.

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- SARS-CoV-2 GMT at each time point and GMFRs from before vaccination to each time point after vaccination, and the proportion of participants with seroresponse at 1, 4, and 8 weeks after vaccination, will be provided for each strain by study intervention group with a BNT162b2 dose, and separately by age group.
- SARS-CoV-2 GMTs for each strain and the associated 95% CIs will be plotted by study intervention group with a BNT162b2 dose, for participants 18 through 64 years of age and ≥65 years of age separately.
- SARS-CoV-2 seroresponse rate for each strain, along with the associated 95% CIs, will be presented by study intervention group with a BNT162b2 dose, for participants 18 through 64 years of age and ≥65 years of age separately.
- Empirical RCDCs with HAI titers and SARS-CoV-2 neutralizing titers will be plotted separately for each strain by study intervention group, for participants 18 through 64 years of age and ≥65 years of age separately.
- Bar charts with the numbers, proportions of participants achieving HAI seroconversion, and associated 95% CIs at 4 weeks after study intervention administration will be provided for each strain by study intervention group with qIRV, for participants 18 through 64 years of age and ≥65 years of age separately.
- Bar charts with the numbers, SARS-CoV-2 seroresponse rate, and associated 95% CI at 4 weeks after study intervention administration will be provided for each strain by study intervention group with a BNT162b2 dose, for participants 18 through 64 years of age and ≥65 years of age separately.

6.2.1.2. Sensitivity/Supplementary Analysis

To support the assessment of immunogenicity, estimands as specified in Section 2.2.2 using the treatment policy strategy may be summarized with the mITT population using the same presentation as specified in the main analysis.

6.3. Other/Exploratory Endpoints

6.3.1. Immunogenicity for Emerging VOCs

6.3.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.3).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis methodology: Descriptive summary statistics (Section 5.2.2).
- Analysis timing: 1, 2, and 4 Weeks after study intervention administration.
- Intercurrent events and missing data: All data collected after or at intercurrent events will not be included; missing data will not be imputed.

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- Reporting results:
  - SARS-CoV-2 VOC GMTs and associated 95% CIs will be provided for VOCs not already specified, by study intervention group with a BNT162b2 dose, for participants 18 through 64 years of age and ≥65 years of age separately.
  - SARS-CoV-2 VOC GMFRs from before vaccination to each time point after vaccination and associated 95% CIs will be provided for VOCs not already specified, by study intervention group with a BNT162b2 dose, for participants 18 through 64 years of age and ≥65 years of age separately.

6.3.2. Immunogenicity Comparisons Between Study Interventions

The GMRs and differences for proportion of participants achieving HAI seroconversion between the following study interventions, with associated 95% CIs, will be provided for each strain, for participants 18 through 64 years of age and ≥65 years of age separately:

- [CCI]µg qIRV [CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5) vs [CCI] µg qIRV
- [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5) vs [CCI]µg qIRV
- [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5) vs [CCI]µg qIRV

The SARS-CoV-2 GMRs and differences for seroresponse rate between the following study interventions, with associated 95% CIs, will be provided for each VOC/strain, for participants 18 through 64 years of age and ≥65 years of age separately:

- [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5) vs [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5)
- [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5) vs [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5)
- [CCI]µg qIRV/[CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5) vs [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5)

The immunogenicity data for [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5) and [CCI]µg bivalent BNT162b2 (original/Omi BA.4/BA.5) from Study C4591044 will be used for these GMRs and comparisons of seroresponses. The immunogenicity data of participants from Study C4591044 with seasonal and pandemic influenza vaccine given at least 14 days after, or at least 14 days prior to, the administration of BNT162b2 will be excluded from the above analyses. In addition, the above analyses might be performed by baseline SARS-CoV-2 infection status (based on N-binding antibody results at Visit 1 before vaccination and medical history of SARS-CoV-2).

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6.4. Subset Analyses

Subgroup analyses, based on baseline SARS-Cov-2 infection status (based on N-binding antibody results at Visit 1 before vaccination and medical history of SARS-CoV-2), will be performed on secondary immunogenicity endpoints by study intervention group with a BNT162b2 dose, as supplemental analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics and Medical History

Descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, ethnicity, and racial designation) 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) will be generated by study intervention group and for all participants in total, for participants 18 through 64 years of age and ≥65 years of age separately and combined, based on the safety population.

Each reported medical history term will be mapped to a SOC and PT according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by study intervention group and for all participants in total, for participants 18 through 64 years of age and ≥65 years of age separately and combined, based on the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

All participants in the mITT population will be included in the disposition summaries. Summaries will be displayed by study intervention, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the number and percentage of participants who received vaccinations, completed the follow-up visits, and withdrew before each follow-up visit phase, along with the reasons for withdrawal, will be tabulated by study intervention group and for the total sample for each age group separately and combined. The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately by study intervention group and age group separately and combined, along with the reasons for exclusion.

A listing of protocol deviations may also be provided.

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6.5.2.2. Blood Samples for Assay

For each blood sampling time point, the number and percentage of randomized participants providing blood samples within the protocol-specified time frame, as well as before and after the protocol-specified time frame, will be tabulated separately by study intervention group and for the total population, for participants 18 through 64 years of age and ≥65 years of age separately.

6.5.2.3. E-Diaries

The participants who were vaccinated and who transmitted and completed e-diaries will be summarized according to the vaccine actually received, for participants 18 through 64 years of age and ≥65 years of age separately and combined. Besides the analysis described in Section 3.4.2, the summary will also include the number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and completing the e-diary for any day in the required reporting period, by assigned study intervention and age group.

The number and percentage of participants transmitting and completing the e-diary for each day in the required reporting period, and overall, will be tabulated for each study intervention group and for the total sample, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

The safety population will be used.

6.5.3. Study Intervention Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving each study intervention will be tabulated for each study intervention group and overall, for all randomized participants 18 through 64 years of age and ≥65 years of age separately and combined. The denominator for the percentages is the total number of participants in the given study intervention group or overall, for each age group. In addition, the relation of the randomized study intervention to the actual study intervention received will be presented as a cross-tabulation of the actual study intervention received versus the randomized study intervention, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

A listing of participants showing the randomized study intervention and the study intervention actually received will be presented.

6.5.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. The prior/concomitant vaccine received before vaccination will be listed. The number and percentage of randomized participants receiving each vaccine after study intervention administration will be tabulated according to the assigned study intervention, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

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6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Local reaction, systemic event, AE, and SAE summaries, clinical safety laboratory assessments (troponin I), and ECG summaries and analyses are described under Primary Endpoints (Section 6.1).

A listing will be generated for all of the participants with unscheduled/unplanned visits because of severe (Grade 3) and Grade 4 reactions.

Descriptive summaries and listings of participants reporting immediate AEs during the protocol-specified ≥30-minute observation period for any acute reactions will be presented by study intervention group, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

In addition, any symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be listed and/or summarized by study intervention group, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

6.6.2. Laboratory Data

Clinical safety laboratory assessment (troponin I) is described under Primary Endpoints.

6.6.3. Vital Signs

A descriptive summary based on the safety population will be provided in accordance with the Pfizer reporting standards, and listings may be generated, for participants 18 through 64 years of age and ≥65 years of age separately and combined.

6.6.4. Electrocardiograms

The ECG summaries and analyses are described under Primary Endpoints.

7. INTERIM ANALYSES

7.1. Introduction

This study will use an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.

7.2. Interim Analyses and Summaries

No formal interim analysis will be conducted for this study. As the study is open label to the sponsor, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

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8. REFERENCES

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

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
APE	analysis population exclusion
ATC	Anatomic Therapeutic Chemical
AV	atrioventricular
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CORD	Clinical Oversight Review Dashboard
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
ICD	informed consent document
IV	intravenous
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein–binding
Omi	Omicron
PIPD	potentially important protocol deviations
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class

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Abbreviation	Term
VOC	variant of concern
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	19-Jan-2023 15:52:13	Business Line Approver

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Protocol C5261001

A PHASE 1/2 MASTER PROTOCOL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF COMBINED MODIFIED RNA VACCINE CANDIDATES AGAINST COVID-19 AND INFLUENZA IN HEALTHY INDIVIDUALS – SUBSTUDY B

Statistical Analysis Plan (SAP)

Version: 2

Date: 22 Feb 2024

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LIST OF TABLES

APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 22 Feb 2024	Amendment 6 09 Feb 2024	To match protocol amendment 6.	Updated various sections to remove references to objectives/endpoints/analyses related to participants 65+ years of age, removed references to initial enrollment groups and expanded enrollment groups throughout, and made the study design section (including the number of participants) consistent with the protocol amendment. Added an additional exploratory objective related to troponin and ECG abnormalities. Excluded the endpoint of achieving HAI seroconversion for all strains and HAI titers ≥1:40 for all strains. Removed references to "first vaccination," "first dose," and "each dose," since only 1 visit in protocol amendment 6 includes vaccination. Removed the 6-month serology secondary endpoint to be consistent with the protocol amendment and made the endpoint wording more consistent with protocol amendment.
		To respond to regulatory feedback.	Provided adjustment on the reporting of reactogenicity, taking into account the occurrence of AEs corresponding to reactogenicity terms within the 7-day reporting period after vaccination. Added GMR and the difference in seroconversion/seroresponse as supplementary analyses.
		To reflect updates in the team decision.	Added an analysis of seroconversion by baseline status.
1 27 Jun 2023	Amendment 4 16 Apr 2023	N/A	N/A

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2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in C5261001 – Substudy B. 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. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Estimands, and Endpoints

The primary, secondary, and tertiary/exploratory objectives, associated estimands, and associated endpoints are described in the following table:

Substudy B (Phase 1/2)

Type	Objectives	Estimands	Endpoints
	Primary Safety	**Primary Safety**	**Primary Safety**
Safety	To describe the safety and tolerability of each study intervention in participants 18 through 64 years of age.	In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants with: • Abnormal troponin I laboratory values 2 days and 1 week after vaccination.	• Troponin I laboratory parameters detailed in Section 3.1.3.
		In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants with: • New ECG abnormalities 2 days and 1 week after vaccination.	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis, as defined in the protocol.
		In participants 18 through 64 years of age receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination in the right arm only. • Systemic events for up to 7 days following vaccination. • AEs from vaccination through 4 weeks after vaccination. • SAEs from vaccination through 6 months after vaccination.	• Local reactions (pain at the injection site, redness, and swelling) in the right arm only. • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). • AEs. • SAEs.

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Substudy B (Phase 1/2)

Type	Objectives	Estimands	Endpoints
Immunogenicity	**Secondary Immunogenicity**[a]	**Secondary Immunogenicity**	**Secondary Immunogenicity**
	To describe the immune responses to SARS-CoV-2 and influenza elicited by each study intervention.	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants): • GMTs before vaccination and at each blood sampling time point after influenza vaccination. • GMFR from before vaccination to each blood sampling time point after influenza vaccination. • The proportion of participants achieving HAI seroconversion[b] for each strain at each blood sampling time point after influenza vaccination. • The percentage of participants with HAI titers ≥1:40 for each strain before vaccination and at each blood sampling time point after influenza vaccination.	• HAI titers for the matched seasonal strains recommended by WHO.
		In participants 18 through 64 years of age complying with key protocol criteria (evaluable participants): • GMTs before vaccination and at each blood sampling time point after vaccination for each strain. • GMFR from before SARS-CoV-2 vaccination to each blood sampling time point after vaccination for each strain. • Percentages of participants with seroresponse[c] at each blood sampling time point after SARS-CoV-2 vaccination for each strain.	• SARS-CoV-2–neutralizing titers by strain.
	Tertiary/Exploratory	**Tertiary/Exploratory**	**Tertiary/Exploratory**
	To describe the immune response to emergent variants (under monitoring, of interest, and/or of concern) in participants 18 through 64 years of age.	As detailed in the SAP (Section 3).	• SARS-CoV-2–neutralizing titers for variants (under monitoring, of interest, and/or of concern).

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Substudy B (Phase 1/2)

Type	Objectives	Estimands	Endpoints
	To describe the troponin and ECG abnormalities detected in participants who are evaluated for possible cardiac symptoms.	As detailed in the SAP (Section 3).	• Troponin I laboratory parameters as detailed in the protocol. • ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol.

a. There are no primary immunogenicity objectives in this study.
b. Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest, or an HAI titer of ≥1:10 prior to vaccination with at least a 4-fold rise at the time point of interest.
c. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.

The estimands to evaluate the safety objective are based on the safety population. These estimands estimate vaccine safety after administration of study intervention. Completely missing e-diary data will not be imputed; missing AE dates will be handled according to Pfizer safety rules.

The estimands to evaluate the immunogenicity objectives are based on the evaluable immunogenicity population. These estimands estimate the immune response after study intervention administration in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing immunogenicity results will not be imputed, as MCAR is assumed.

Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the GMT analyses.

2.3. Study Design

This is a Phase 1/2 substudy to describe the safety, tolerability, and immunogenicity of IRV (qIRV, tIRV, or bIRV) when administered in combination with bivalent BNT162b2 (original/Omi BA.4/BA.5). Bivalent BNT162b2 (original/Omi BA.4/BA.5) will be used during the substudy, as detailed in Table 7. Substudy B will be single-blind (sponsor unblinded). In Substudy B, up to approximately 630 participants 18 through 64 years of age will be enrolled.

Randomization will be conducted across 3 enrollment cohorts independently due to licensed QIV availability, with enrollment in these cohorts being conducted either concurrently or at different times as required based on operational considerations as shown in Table 2.

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Table 2. Substudy B: Enrollment Cohorts

Enrollment Cohort	Total Number of Participants	Number of Participants per Vaccine Group	Vaccine Group Number	Vaccine Group Descriptions
1	60	30	1	Licensed QIV (Flucelvax) administered concurrently in the opposite arm to [CCI]µg bivalent BNT162b2 (original*/Omi BA.4/BA.5)
			2	Licensed QIV (Flucelvax) administered concurrently in the opposite arm to bIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)
2	360	Up to 120	3	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 1[a]
			4	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 2[a]
			5	qIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5) at dose-level combination 3[a]
3	210	30	6	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 4[a]
			7	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 5[a]
			8	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 6[a]
			9	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 7[a]
			10	qIRV/bivalent BNT162b2 (original/ Omi BA.4/BA.5) at dose-level combination 8[a]
			11	tIRV/bivalent BNT162b2 (original/Omi BA.4/BA.5)
			12	qIRV

a. Note: Combinations as shown in Table 7.
Note: * Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in the protocol as the reference strain.

All participants will be asked to complete a reactogenicity e-diary for 7 days following vaccination.

Blood samples will be collected for immunogenicity assessments prior to vaccination and at 4 weeks after vaccination in Substudy B.

Following vaccination, AEs will be collected from informed consent signing through 4 weeks following vaccination, and SAEs will be collected from informed consent signing through 6 months after vaccination. In addition, AEs will be collected that occur up to 48 hours after blood draws.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Abnormal troponin I laboratory values 2 days and 1 week after vaccination.
- New ECG abnormalities 2 days and 1 week after vaccination.
- Local reactions for up to 7 days following vaccination.
- Systemic events for up to 7 days following vaccination.
- AEs from vaccination through 4 weeks after vaccination.
- SAEs from vaccination through 6 months after vaccination.

3.1.1. Local Reactions and Systemic Events

Local reactions will be assessed at the injection site on the right arm only. Endpoints include both each reaction or event and any reaction or event.

The local reactions, including redness, swelling, and pain at the injection site, and the systemic events, including fever, fatigue (tiredness), headache, muscle pain, vomiting, diarrhea, chills, and joint pain, are reported in the e-diary from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination. The e-diary entries from the participant will be the primary data source for these events. However, any related events that are considered local reactions or systemic events starting within 7 days after vaccination, that are recorded in the unplanned CRF or AE CRF, will be consolidated with e-diary data and the data included in the reactogenicity summaries if the participant has any e-diary data recorded.

This section describes derivations with details for the assessment of the reactogenicity data: severity level, duration, and onset day.

Severity and Maximum Severity

The definitions for reactogenicity severity collected from the e-diary and from AEs are described in Appendix 2.

For each local reaction or systemic event after vaccination, the maximum severity will be derived for the collection period (Day 1 through Day 7, where Day 1 is the day of vaccination) as follows:

> maximum severity = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades reported for that local reaction or systemic event

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Duration (First to Last Day Reported)

The duration (days) of each local reaction or systemic event will be calculated as the number of days from the start of the first reported reaction or event to the resolution of the last reported reaction or event, inclusive. For reactions or events collected in the e-diary, resolution is defined as the last day on which the reaction or event is recorded in the e-diary if the reaction or event lasted 7 days or less, or it is defined as the day on which the reaction or event ended beyond Day 7 (the latter will be collected on the CRF). For reactions and events collected in the AE CRF, the AE end date will be considered the resolution date. For a reaction or event collected in multiple sources, the latest date will be used in calculating the duration. If there is no known resolution/end date, the duration will be reported as unknown or missing.

Onset Day

The onset day of each local reaction or systemic event will be derived. Onset day is defined as the first day of reporting the reaction or event with any severity after study intervention administration. For a reaction or event collected in multiple sources, the earliest reported date of the reaction will be used in calculating the onset day.

Presence will be derived for each day and any day.

Use of Antipyretic/Pain Medication

The use of antipyretic/pain medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of vaccination. For the use of antipyretic/pain medication from Day 1 through Day 7, the following endpoint and variable will be derived:

- Presence (yes or no) of use of antipyretic/pain medication after vaccination (on any day and for each day).

3.1.2. Adverse Events

Standard algorithms for handling missing AE dates will be applied (see Section 5.3). AEs will be categorized according to MedDRA terms. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study through the 4-week follow-up visit. Additionally, any AEs occurring up to 48 hours after the blood draws at Visit 204 (4-week follow-up visit) must be recorded on the CRF.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the participant's study vaccination.

Events occurring prior to vaccination will be excluded from the AE analyses but may be listed out.

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3.1.3. Laboratory Data

The following safety laboratory test will be performed at the times defined in the schedule of activities of the protocol.

Substudy B Enrollment	
Hematology	**Chemistry**
N/A	Cardiac troponin I

Clinically significant abnormal laboratory findings should be recorded in the AE CRF. Any troponin I value ≥0.30 ng/mL is considered abnormal.

3.1.4. ECG Data

ECGs will be collected at the times specified for the substudy.

ECG data will be submitted to a central laboratory for evaluation.

ECG abnormalities consistent with probable or possible myocarditis or pericarditis are those judged as such by a cardiologist.

3.2. Secondary Endpoints

Blood samples will be collected for immunogenicity assessments prior to vaccination and at 4 weeks after vaccination.

Influenza

- HAI titers for each strain before vaccination and at each time point after vaccination.
- HAI titer fold rises for each strain from before vaccination to each time point after vaccination.
- HAI seroconversion for each strain at each time point after vaccination.
- HAI titers ≥1:40 for each strain before vaccination and at each time point after vaccination.

Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest or an HAI titer of ≥1:10 prior to vaccination with at least a 4-fold rise at the time point of interest.

Fold rises are defined as ratios of the results after vaccination to the results before vaccination. The calculations of fold rises are limited to participants with nonmissing values at both time points.

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The strains mentioned above for qIRV- or QIV-related study interventions refer to the matched seasonal strains ([redacted] and ([redacted] recommended by WHO, and the strains mentioned above for tIRV-related study interventions refer to the matched seasonal strains ([redacted] recommended by WHO.

SARS-CoV-2

- SARS-CoV-2–neutralizing titers for each strain before vaccination and at each time point after vaccination.
- SARS-CoV-2–neutralizing titer fold rise for each strain from before vaccination to each time point after vaccination.
- SARS-CoV-2 seroresponse for each strain at each time point after vaccination.

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

The strain mentioned above refers to SARS-CoV-2 (Omi BA.4/BA.5) or the SARS-CoV-2 reference strain (original).

Fold rises are defined as ratios of the results after vaccination to the results before vaccination. The calculations of fold rises are limited to participants with nonmissing values at both time points.

3.3. Other Endpoints

- SARS-CoV-2–neutralizing titers for each strain of emergent variants at each time point.
- SARS-CoV-2–neutralizing titer fold rise for each strain of emergent variants from before vaccination to each time point after vaccination.
- SARS-CoV-2 seroresponse for each strain of emergent variants at each time point after vaccination.

3.4. Baseline Variables

Age at the time of vaccination (in years) will be derived based on the participant's birthday. For example, if the vaccination day is 1 day before the participant's 19th birthday, the participant is 18 years old.

For reporting of race, where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Medical history will be categorized according to MedDRA.

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The name and date of administration for any concomitant medications and nonstudy vaccinations received will be collected.

3.4.1. E-Diary Completion

An e-diary will be considered transmitted if any data for the 3 local reactions (redness, swelling, and pain at the injection site), 8 systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsening muscle pain, and new or worsening joint pain), or use of antipyretic/pain medication to treat symptoms, are present on any day. If all data are missing for all items on the e-diary, for all days following vaccination, the e-diary will be considered not transmitted.

An e-diary will be considered completed if all expected data for all days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

The following e-diary compliance variables will be provided:

- Compliance per day: The numerator is the number of participants who completed (transmitted) the e-diary on a given day (Day 1 through Day 7, where Day 1 is the day of vaccination) and the denominator is the total number of participants who received the vaccination.

- At least X days: The numerator is the number of participants who completed (transmitted) the e-diary on X days and the denominator is the total number of participants who received a vaccination (X = Day 1 through Day 7; compliance will be computed for each value of X).

- All 7 days: The numerator is the number of participants who completed (transmitted) the e-diary on all 7 days and the denominator is the total number of participants who received a vaccination.

3.5. Safety Endpoints

Refer to Section 3.1.

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 standard operating procedures.

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.

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Population	Description
Evaluable immunogenicity	All participants who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame after vaccination (26-35 days after vaccination), have at least 1 valid and determinate assay result at the 4-week postvaccination visit, and have no major protocol violations.
mITT immunogenicity	All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result after vaccination.
Safety	All participants who receive the study intervention.

For determination of the evaluable immunogenicity population(s), the last criteria of exclusions due to major protocol violations will be determined via clinical review. The remainder of the criteria will be determined programmatically.

A major protocol violation is a protocol violation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine, medication that might affect immune response, or a medication error with suspected decrease in potency of the vaccine. The global medical monitor from the sponsor will identify those participants with a protocol violation prior to any immunogenicity analysis in the study.

For safety, reporting will be as administered and, for immunogenicity, reporting will be as randomized.

For all the immunogenicity endpoints, the analysis will be based on the evaluable immunogenicity population.

An additional analysis may be performed based on the mITT population if there is a large enough difference (>10%) in sample size between the mITT population and the evaluable immunogenicity population.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no hypotheses and decision rules defined for the study. A descriptive estimation approach will be used to assess all study objectives in the study. Point estimates and nominal 95% CIs will be provided for all safety and immunogenicity endpoints at each planned analysis. No formal multiplicity adjustments will be applied due to multiple endpoints or multiple evaluations for the same endpoint.

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.

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5.2.1. Analyses for Binary Endpoints

Descriptive statistics for binary 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 Clopper-Pearson method.[1]

For the between-group difference, the 2-sided 95% CI will be calculated using the Miettinen and Nurminen method.

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

5.2.2.2. Geometric Mean Ratio

Unadjusted GMR

The GMR will be calculated as the difference in the means of logarithmically transformed assay results between 2 vaccine groups and exponentiating the difference. The 2-sided 95% CI will be obtained by exponentiating the limits of the CI for the mean difference of the logarithmically transformed assay results based on the Student t distribution.

Model-Based GMR

A linear regression model, including the log baseline titer as a covariate, will be used to analyze the titers after log transformation. The GMR and the 2-sided 95% CI will be calculated by exponentiating the difference in LS means and corresponding CI estimated from the regression model.

5.2.2.3. Geometric Mean Fold Rises

The GMFR for each vaccine group is defined as the geometric mean of the fold rises in the assay results from the specified time points. Only data from participants with nonmissing assay results at both time points will be included in the GMFR calculation.

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 the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

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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 the line first going down and then to the right to the next assay value.

5.3. Methods to Manage Missing Data

Standard algorithms on handling missing AE dates will be applied according to Pfizer safety rules. A completely missing start date for an AE is not allowed in data collection. For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Day 1 through Day 7)" data will be considered nonmissing. It is expected that these reactogenicity events would be queried by the investigator for the missing e-diary days and would be entered in the AE CRF if any reactogenicity was not reported in the e-diary due to missed days. Therefore, the primary analysis will use the reactogenicity recorded in the AE CRF to impute the partially missing e-diary data to estimate the reactogenicity rate during the e-diary collection period. The AE CRF is designed as a log page, which means only events that occurred will be recorded and events that did not occur will not be recorded. Therefore, all remaining missing days are considered as having answered "no." This imputation can reasonably estimate the reactogenicity event rates during the e-diary collection period.

Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses.

When calculating a fold rise, the assay results will be converted to 0.5 × LLOQ if assay results are < LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

Values for sera that are insufficient, indeterminate results, or values recorded as "not done" will be set to "missing."

LLOQs for each assay used in this study will be included in serology data transfer once they are available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Local Reactions and Systemic Events

6.1.1.1. Main Analysis

- Estimand: The proportion of participants reporting local reactions and systemic events within 7 days after vaccination (Section 2.2).

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- Analysis set: Safety population (Section 4) for participants with any e-diary data through 7 days.
- Analysis time point: Within 7 days after vaccination (Section 3.1).
- Analysis methodology: 95% CI of the proportion of participants reporting each reaction or event using the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive statistics including counts, point estimates, and the associated exact 2-sided 95% CIs using the Clopper-Pearson method for the proportion of participants 18 through 64 years of age reporting each (and any) reaction or event for each vaccine group. The denominator used in the proportion calculation will be the number of participants with any reactogenicity data reported after vaccination.

6.1.1.2. Sensitivity/Supplementary Analyses

To support the assessment of reactogenicity, the endpoints will be summarized with the same analysis time points and analysis population:

- Duration (days) of each local reaction and each systemic event after vaccination.
- Onset day of each local reaction and each systemic event after vaccination.
- Presence of each local reaction and each systemic event, for "any day (Day 1 through Day 7)." Any severe local reactions or any severe systemic events for "any day (Day 1 through Day 7)."
- The proportion of participants reporting local reactions and systemic events within 7 days after vaccination based only on e-diary data. These continuous endpoints will be summarized by displaying the n, mean, median, standard deviation, minimum, and maximum for each study intervention group for participants 18 through 64 years of age.

Summaries of the proportion of participants with each local reaction and systemic event occurring within 7 days of vaccination (by maximum severity) will also be created using bar charts.

6.1.2. AEs and SAEs

6.1.2.1. Main Analysis

- Estimand: The proportion of participants reporting AEs from vaccination through 4 weeks after vaccination and SAEs from vaccination through 6 months after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).

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- Analysis time point: From vaccination through 4 weeks after vaccination for AEs and from vaccination through 6 months after vaccination for SAEs (Section 3.1).

- Analysis methodology: 95% CI of the proportion of participants reporting each AE/SAE using the Clopper-Pearson method (Section 5.2.1).

- Intercurrent events and missing data: Missing values will not be imputed except for partially missing dates (Section 5.3).

- Reporting results: Descriptive statistics, including counts, point estimates, and the associated exact 2-sided 95% CIs using the Clopper-Pearson method, for the proportion of participants reporting AEs from vaccination through 4 weeks after vaccination for each vaccine group, for participants 18 through 64 years of age.

- Reporting results: Descriptive statistics, including counts, point estimates, and the associated exact 2-sided 95% CIs using the Clopper-Pearson method, for the proportion of participants reporting SAEs from vaccination through 6 months after vaccination for each vaccine group, for participants 18 through 64 years of age.

6.1.2.2. Sensitivity/Supplementary Analysis

The proportion of participants reporting AEs (which includes reactogenicity events collected in the AE CRF during the e-diary collection period) from vaccination through 4 weeks after vaccination will be provided as a sensitivity analysis.

Additional analyses will include summaries of AE/SAEs by SOC and PT. Furthermore, descriptive summaries may be done for different types of AEs (eg, related AEs, severe AEs, immediate AEs, AEs leading to discontinuations, etc). Additionally, any AEs occurring up to 48 hours after the blood draws at the 4-week follow-up visit will be summarized descriptively or included in the listing.

6.1.3. Laboratory Data

6.1.3.1. Main Analysis

- Estimand: The proportion of participants reporting abnormal troponin I laboratory values for each study intervention group at 2 days and 1 week after vaccination (Section 2.2).

- Analysis set: Safety population (Section 4).

- Analysis time point: At 2 days (visit window 2 to 4 days) and 1 week (visit window 6 to 8 days) after vaccination (Section 3.1).

- Analysis methodology: 95% CI of the proportion of participants reporting abnormal troponin I laboratory values using the Clopper-Pearson method (Section 5.2.1).

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- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive statistics, including counts, point estimates, and the associated exact 2-sided 95% CIs using the Clopper-Pearson method, for the proportion of participants reporting abnormal troponin I laboratory values for each vaccine group at 2 days and 1 week after vaccination (within windows), for participants 18 through 64 years of age.

6.1.3.2. Sensitivity/Supplementary Analysis

Not applicable.

6.1.4. ECG Data

6.1.4.1. Main Analysis

- Estimand: The proportion of participants reporting new ECG abnormalities for each study intervention group at 2 days and 1 week after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: At 2 days (visit window 2 to 4 days) and 1 week (visit window 6 to 8 days) after vaccination (Section 3.1).
- Analysis methodology: 95% CI of the proportion of participants reporting new ECG abnormalities using the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Descriptive statistics, including counts, point estimates, and the associated exact 2-sided 95% CIs using the Clopper-Pearson method, for the proportion of participants reporting new ECG abnormalities for each vaccine group at 2 days and 1 week after vaccination (within windows), for participants 18 through 64 years of age.

6.1.4.2. Sensitivity/Supplementary Analysis

Not applicable.

6.2. Secondary Endpoints

6.2.1. Immunogenicity Endpoints

6.2.1.1. Main Analysis

- Estimands: All immunogenicity estimands (including seroconversion/seropositive percentages, GMTs, and GMFRs) for secondary endpoints (Section 2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).

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- Analysis time point: At each blood sampling time point (at baseline, 4 weeks after vaccination). GMFRs, seroconversion percentages, and seroresponse percentages can only be reported out for postvaccination time points (Section 3.2).

- Analysis methodology: Descriptive statistics including 95% CIs as per Section 5.2.

- Intercurrent events and missing data: Antibody titers below the LLOQ will be treated as specified in Section 5.3. Missing data will not be imputed.

- Reporting results:

  Influenza:

  - Descriptive statistics, including the sample size (n), HAI GMTs, GMFRs, and 95% CI for the HAI GMTs and GMFRs, will be presented for each strain by study intervention group.

  - The proportion of participants achieving HAI seroconversion and the associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain by study intervention group.

  - The proportion of participants with HAI titers ≥1:40 and the associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain by study intervention group.

  - Seroconversion proportions, GMTs, and GMFRs may be plotted by study intervention group.

  SARS-CoV-2:

  - The SARS-CoV-2 GMT, GMFRs, and the proportion of participants with seroresponse will be estimated for each strain by study intervention group.

  - Seroresponse proportions, GMTs, and GMFRs may be plotted by study intervention group.

6.2.1.2. Sensitivity/Supplementary Analysis

- Empirical RCDCs with HAI titers and SARS-CoV-2–neutralizing titers will be plotted separately for each strain by study intervention group.

- Additional analyses may be performed based on the mITT population if there is a large enough difference (>10%) in sample size between the mITT population and the evaluable immunogenicity population.

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- The difference in the proportion of participants achieving HAI seroconversion between each study intervention group and comparator group (Group 1 and Group 12) at 4 weeks after vaccination will be provided for each strain.

- The difference in the proportion of participants achieving SARS-CoV-2 seroresponse between each study intervention group and the comparator group (Group 1) at 4 weeks after vaccination will be provided for each strain.

- The unadjusted and baseline titer–adjusted GMR of strain-specific HAI titers between each study intervention group and comparator group (Group 1 and Group 12) at 4 weeks after vaccination will be provided for each strain.

- The unadjusted and baseline titers–adjusted GMR of SARS-CoV-2–neutralizing titers between each study intervention group and the comparator group (Group 1) at 4 weeks after vaccination will be provided for each strain.

6.3. Subset Analyses

Subgroup analyses based on baseline SARS-CoV-2 infection status will be performed for the secondary SARS-CoV-2 immunogenicity endpoints, by study intervention group. Subgroup analyses based on baseline HAI titer value will be performed for the HAI seroconversion endpoint. No subset analyses are planned by sex, race, or ethnicity.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Tertiary/Exploratory Endpoints

The exploratory endpoints in Section 3.3 may be summarized using the same populations and methods as for the secondary endpoints:

- SARS-CoV-2 VOC GMTs and the associated 95% CIs will be provided for VOCs not already specified, by study intervention group, for participants 18 through 64 years of age.

- SARS-CoV-2 VOC GMFRs from before vaccination to each time point after vaccination, and the associated 95% CIs, will be provided for VOCs not already specified, by study intervention group, for participants 18 through 64 years of age.

- SARS-CoV-2 VOC seroresponses at each time point after vaccination, and the associated 95% CIs, will be provided for VOCs not already specified, by study intervention group, for participants 18 through 64 years of age.

In addition, the participants who reported at least 1 symptom indicative of myocarditis or pericarditis within 4 weeks after vaccination will be summarized descriptively.

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6.4.2. Baseline Summaries

Descriptive summary statistics for demographic characteristics and medical history of SARS-CoV-2 will be generated by study intervention group, for participants 18 through 64 years of age, based on the safety population.

Each reported medical history term will be mapped to a SOC and PT according to MedDRA.

6.4.3. Study Conduct and Participant Disposition

6.4.3.1. Participant Disposition

All randomized participants will be included in the disposition summaries. Summaries will be displayed by study intervention group for participants 18 through 64 years of age.

The number of randomized participants will be included in the participant disposition summary. In addition, the number and percentage of participants who received vaccinations, completed the follow-up visits, and withdrew from the study, along with the reasons for withdrawal, will be tabulated by study intervention group.

Participants excluded from each analysis population will also be summarized by study intervention group and age stratum separately along with the reasons for exclusion (eg, for the evaluable immunogenicity population).

6.4.3.2. Blood Samples for Assay

For each blood sampling time point, the number and percentage of randomized participants providing blood samples within the protocol-specified time frame, as well as before and after the protocol-specified time frame, will be tabulated by study intervention group for participants 18 through 64 years of age.

6.4.3.3. E-Diaries

E-diary compliance as defined in Section 3.4.1 will be summarized using descriptive statistics. The safety population will be used to generate the summary reports. The denominator for the e-diary compliance rates will be the total number of participants who received the specific vaccination.

6.4.4. Study Intervention Exposure

The number and percentage of participants randomized and receiving each study intervention will be tabulated by study intervention group for all randomized participants 18 through 64 years of age. In addition, the relation of the randomized study intervention to the actual study intervention received will be presented as a cross-tabulation of the actual study intervention received versus the randomized study intervention for participants 18 through 64 years of age.

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6.5. Safety Summaries and Analyses

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by study intervention.

6.5.1. Adverse Events

The planned analyses for AEs and SAEs are outlined in Section 6.1.2.

6.5.2. Laboratory Data

The planned analyses for laboratory data are outlined in Section 6.1.3.

6.5.3. Electrocardiograms

The planned analyses for ECGs are outlined in Section 6.1.4.

7. INTERIM ANALYSES

7.1. Introduction

This study will use an IRC, an internal Pfizer committee that will review data. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.

Statistical analyses will be carried out when the final data for specified objectives are available while the study is ongoing. The timing of these planned analysis and reporting events is described in Section 7.1.1 below.

7.1.1. Analysis Timings

Analyses (immunogenicity or safety) may be performed at any time (eg, safety data through approximately 1 week after vaccination) for participants 18 through 64 years of age.

Complete safety and immunogenicity analyses will be performed at the end of this substudy.

7.2. Interim Analyses and Summaries

No formal interim analysis will be conducted for this study.

8. REFERENCE

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
bIRV	bivalent influenza modRNA vaccine
BLQ	below the limit of quantitation
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
ICD	informed consent document
IPM	investigational product manual
IRC	internal review committee
IRT	interactive response technology
IRV	influenza modRNA vaccine
IV	intravenous
LLOQ	lower limit of quantitation
LOD	limit of detection
LS	least square
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
Omi	Omicron
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
tIRV	trivalent influenza modRNA vaccine
VOC	variant of concern
WHO	World Health Organization

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Appendix 2. Reactogenicity Data Consolidation

For reactogenicity collected in the e-diary, redness and swelling will be measured and recorded in measuring device (caliper) units, and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 3. Measuring device units can be converted to centimeters according to the following scale: 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 3. The systemic events of fatigue (tiredness), headache, muscle pain, vomiting, diarrhea, chills, and joint pain will be assessed by participants as mild, moderate, or severe according to the grading scale in Table 4. Grade 4 reactions and events, which can only be classified by an investigator or medically qualified person, will be collected as AEs on the CRF. For reactogenicity collected in the AE CRF, the grading scales will be based on the AE intensity scale in Table 5. If a local reaction or systemic event is captured in more than 1 data source, eg, the e-diary, unplanned assessments, and/or AE CRF, the highest grade will be used in the safety summary analysis.

Table 3. Local Reaction Grading Scale

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

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue

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Table 4. Systemic Event Grading Scale

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

Table 5. Assessment of AE Intensity Grade

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius first for reporting. Fever will be grouped into ranges for the analysis according to Table 6. Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 6 for summary of maximum temperature.

Table 6. Scale for Fever

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

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Appendix 3. Dose-Level Combinations for Substudy B

Table 7. Substudy B: qIRV Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combination

Dose-Level Combination	qIRV Dose and Strain Combination	Bivalent BNT162b2 (Original*/Omi BA.4/BA.5) Dose[a]	Total modRNA Dose
1[b]	CCI µg **qIRV** containing CCI	CCI µg	CCI µg
2[d]	CCI µg qIRV containing CCI	µg	µg
3[b]	CCI µg qIRV containing CCI	µg	µg
4[b]	CCI µg qIRV containing CCI	µg	µg
5[b]	CCI µg, qIRV containing CCI	µg	µg

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Table 7. Substudy B: qIRV Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Dose-Level Combination

Dose-Level Combination	qIRV Dose and Strain Combination	Bivalent BNT162b2 (Original*/Omi BA.4/BA.5) Dose[a]	Total modRNA Dose
6[b]	CCI µg qIRV containing CCI	CCI µg	CCI µg
7[b]	CCI µg qIRV containing CCI	µg	µg
8[b]	CCI µg qIRV containing CCI	µg	µg

a. For bivalent BNT162b2 formulations: CCI µg total dose includes CCI µg of Omi BA.4/BA.5 and CCI µg of the ancestral SARS-CoV-2 strain; CCI µg total dose includes CCI µg of Omi BA.4/BA.5 and CCI µg of the ancestral SARS-CoV-2 strain.

b. mIRVs encoding HA for each A and B strain will be CCI to generate qIRV at the dose-level combination shown; the resultant qIRV will then be CCI with bivalent BNT162b2 (original/Omi BA.4/BA.5) prior to administration. Please see the IPM for further details.

c. This A strain will be updated to CCI based on the 2023-2024 northern hemisphere seasonal influenza strain selection.

d. CCI product.

Note: * Original refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in the protocol as the reference strain.

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