Protocol C4781001 – Substudy B

A PHASE 1/2 RANDOMIZED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MODIFIED RNA VACCINE AGAINST INFLUENZA IN HEALTHY INDIVIDUALS – SUBSTUDY B

Statistical Analysis Plan (SAP)

Version: 3

Date: 27 Jul 2022

[redacted]

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CCI [redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
3/ 27 Jul 2022	Final protocol amendment 5, 03 Jul 2022	1. Made minor revisions to the study design and corresponding objectives, estimands, and endpoints to reflect the changes made to the protocol amendment. 2. Updated the study design to add the age group 18 through 64 years. 3. Added the secondary and tertiary objectives, estimands, and endpoints for the age group 18 through 64 years. 4. CCI [redacted] 5. Changed the time period of the prohibited nonstudy influenza vaccination. 6. Revised text to adjust analyses as appropriate for the addition of the 18- through 64-year age group.	1. Changed Section 2.1 2. Changed Section 2.3.1 3. Changed Section 2.2.2, Section 2.2.3, Section 6.2.1.1, Section 6.2.1.2, Section 6.2.2.1, Section 6.2.2.2, Section 6.3.1.1, and Section 6.3.1.2 4. Changed Section 2.2.3.1 5. Changed Section 3.4.3 6. Changed Section 6.5.1.1, Section 6.5.2.2, Section 6.5.4, and Section 6.6
2/ 15 Mar 2022	Final protocol amendment 4, 08 Feb 2022	• Updated to new SAP template • Study design, updated number of participants and added additional vaccine groups • Removed microneutralization objective and estimands	• Added Section 2.1 • Changed Sections 2.2, 6.1, 6.2, and 6.3 • Changed Section 2.3 • Deleted original Sections 2.1.6.2 and 6.3.2 • Changed Section 3.3.1
1/ 18 Feb 2022	Final protocol amendment 3, 13 Jan 2022	Not applicable	Not applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4781001 – 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

The following modifications were made: added 240 participants from 18 through 64 years of age, who will receive either 1 dose of CCI qIRV or 1 dose of CCI qIRV; added the primary safety, secondary, and tertiary objectives of immune responses elicited by qIRV in adults from 18 through 64 years of age and their corresponding estimands and endpoints; and removed the tertiary estimands and endpoints for all the heterologous strains.

2.2. Study Objectives, Endpoints, and Estimands

Substudy B (Phase 1/2)

Type	Objectives	Estimands	Endpoints
Primary safety	To describe the safety and tolerability of modRNA influenza vaccines when administered in differing vaccination schedules in adults 18 to 64 and 65 to 85 years of age	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each vaccination • Systemic events for up to 7 days following each vaccination • AEs from the first vaccination to 4 weeks after the last vaccination • SAEs from the first vaccination to 6 months after the last vaccination The percentage of participants with: • Abnormal troponin I laboratory values 2 days after the last vaccination The percentage of participants with: • New ECG abnormalities 2 days after the last 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 Troponin I laboratory parameters ECG abnormalities consistent with probable or possible myocarditis or pericarditis
Secondary immune responses	To describe the immune responses elicited by modRNA influenza vaccines when administered in differing vaccination schedules in adults 65 to 85 years of age	In participants complying with the key protocol criteria (evaluable participants) at Day 21 (if applicable) and 1, 4, and 8 weeks after receipt of the last vaccination: • HAI GMTs before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination • HAI GMFR from before Vaccination 1 to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after receipt of the last vaccination • The proportion of participants achieving HAI seroconversion for each strain prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination • The proportion of participants with HAI titers ≥1:40 for each strain before Vaccinations 1 and 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination	HAI titers for each strain targeted by the study vaccine

Type	Objectives	Estimands	Endpoints
		In participants who have received at least 1 dose of a quadrivalent vaccine, complying with the key protocol criteria (evaluable participants), at Day 21 (if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination: • The proportion of participants achieving HAI seroconversion for all strains prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination • The proportion of participants with HAI titers ≥1:40 for all strains before Vaccinations 1 and 2 (Day 21, if applicable) and 1, 4, and 8 weeks after receipt of the last vaccination	HAI titers for each strain targeted by the study vaccine
	To describe the immune responses elicited by qIRV in adults 18 to 64 years of age	In participants complying with the key protocol criteria (evaluable participants) at 1, 4, and 8 weeks after receipt of vaccination: • HAI GMTs before vaccination and at 1, 4, and 8 weeks after receipt of vaccination • HAI GMFR from before vaccination to 1, 4, and 8 weeks after receipt of vaccination • The proportion of participants achieving HAI seroconversion for each strain at 1, 4, and 8 weeks after receipt of vaccination • The proportion of participants with HAI titers ≥1:40 for each strain before vaccination and at 1, 4, and 8 weeks after receipt of vaccination • The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of vaccination • The proportion of participants with HAI titers ≥1:40 for all strains before vaccination and 1, 4, and 8 weeks after receipt of vaccination	HAI titers for each strain targeted by the study vaccine

Type	Objectives	Estimands	Endpoints
CCI			

2.2.1. Primary Safety Estimands

The primary estimands for the primary objective will follow the treatment policy strategy from the EMA ICH E9 (R1) addendum[1] and estimate the safety percentages regardless of the occurrence of intercurrent event(s) or rescue medication use. The analyses will be based on the actual vaccine received.

In participants receiving at least 1 dose of study intervention:

- The percentage of participants reporting prompted local reactions up to 7 days following each vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules as defined in Section 4.
  - Variable: Presence/absence of prespecified local reactions up to 7 days after each vaccination.
  - Intercurrent event(s): For participants who discontinue receipt of study intervention or discontinue participation in the study.
  - Population-level summary: Percentage and associated 2-sided 95% CI of participants reporting local reactions in each vaccine group.

- The percentage of participants reporting prompted systemic events up to 7 days following each vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules as defined in Section 4.
  - Variable: Presence/absence of prespecified systemic events up to 7 days after each vaccination.
  - Intercurrent event(s): Participants discontinue.

- Population-level summary: Percentage and associated 2-sided 95% CI of participants reporting systemic events in each vaccine group.

- The percentage of participants reporting AEs from the first vaccination to 4 weeks after the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Safety population as defined in Section 4.
  - Variable: Presence of AEs from the first vaccination to 4 weeks after the last vaccination.
  - Intercurrent event(s): Participants discontinue.
  - Population-level summary: Percentage and associated 2-sided 95% CI of participants reporting AEs from the first vaccination to 4 weeks after the last vaccination in each vaccine group.

- The percentage of participants reporting SAEs from the first vaccination to 6 months after the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Safety population as defined in Section 4.
  - Variable: Presence of SAEs from the first vaccination to 6 months after the last vaccination.
  - Intercurrent event(s): Participants discontinue.
  - Population-level summary: Percentage and associated 2-sided 95% CI of participants reporting SAEs from the first vaccination to 6 months after the last vaccination in each vaccine group.

- The percentage of participants with abnormal troponin I laboratory values 2 days after the last vaccination.

This estimand includes the following attributes:

- Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
- Population: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules as defined in Section 4.
- Variable: Presence of abnormal troponin I laboratory values 2 days after the last vaccination. A troponin I value >0.3 µg/L is considered abnormal as per the reference range of the contracted vendor laboratory.
- Intercurrent event(s): Participants discontinue.
- Population-level summary: Percentage and associated 2-sided 95% CI of participants with abnormal troponin I laboratory values 2 days after the last vaccination in each vaccine group.

- The percentage of participants with new ECG abnormalities 2 days after the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules as defined in Section 4.
  - Variable: Presence of new ECG abnormalities (as defined in Section 3.1.1.7) 2 days after the last vaccination.
  - Intercurrent event(s): Participants discontinue.
  - Population-level summary: Percentage and associated 2-sided 95% CI of participants with new ECG abnormalities 2 days after the last vaccination in each vaccine group.

2.2.2. Secondary Estimands

For the purposes of the study, the following also applies to the tertiary/exploratory estimands:

- 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 ≥1:10 prior to vaccination with a 4-fold rise at the time point of interest.

The secondary estimands for the secondary objective will use the hypothetical strategies from the EMA ICH E9 (R1) addendum[1] and estimate the immune response.

2.2.2.1. HAI Titers for Each Strain Targeted by the Study Vaccine for Each Strain

2.2.2.1.1. Participants From 65 Through 85 Years of Age

- HAI GMTs before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Evaluable immunogenicity population as defined in Section 4.
  - Variable: HAI GMTs on Day 1 prior to Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.
  - Intercurrent event(s): For participants who discontinue, have major protocol violations, and/or results obtained from out-of-window blood draws. The windows of blood draws, as mentioned throughout the SAP, refer to the assay windows defined in Section 4 in this SAP.
  - Population-level summary: HAI GMTs and associated 2-sided 95% CI for each strain from before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of Vaccination 2.

- HAI GMFRs from before Vaccination 1 to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after receipt of the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Evaluable immunogenicity population as defined in Section 4.
  - Variable: GMFRs from before Vaccination 1 to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after receipt of the last vaccination.
  - Intercurrent event(s): For participants who discontinue, have major protocol violations, and/or results obtained from out-of-window blood draws.

- Population-level summary: HAI GMFRs and associated 2-sided 95% CI for each strain from before Vaccination 1 to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after the last vaccination.

- The proportion of participants achieving HAI seroconversion for each strain prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Evaluable immunogenicity population as defined in Section 4.
  - Variable: Presence of participants achieving HAI seroconversion for each strain prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.
  - Intercurrent event(s): For participants who discontinue, have major protocol violations, and/or results obtained from out-of-window blood draws.
  - Population-level summary: The proportion of participants achieving HAI seroconversion for each strain and associated 2-sided 95% CIs, by vaccine group, prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.

- The proportion of participants with HAI titers ≥1:40 for each strain before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
  - Population: Evaluable immunogenicity population as defined in Section 4.
  - Variable: Presence of participants with HAI titers ≥1:40 for each strain before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.
  - Intercurrent event(s): For participants who discontinue, have major protocol violations, and/or results obtained from out-of-window blood draws.

- Population-level summary: The proportion of participants with HAI titers ≥1:40 for each strain and associated 2-sided 95% CIs, by vaccine group, before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.

2.2.2.1.2. Participants From 18 Through 64 Years of Age

In participants from 18 through 64 years of age, the estimands will be defined and analyzed similarly as above. The time points will be adjusted to 1, 4, and 8 weeks after receipt of vaccination. The baseline will be before vaccination.

2.2.2.2. HAI Titers for Each Strain Targeted by the Study Vaccine for All Strains

2.2.2.2.1. Participants From 65 Through 85 Years of Age

- In participants from 65 through 85 years of age, the following estimands are for those who have received at least 1 dose of a quadrivalent vaccine.

- The proportion of participants achieving HAI seroconversion for all strains prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.

  This estimand includes the following attributes:

  - Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.

  - Population: Evaluable immunogenicity population as defined in Section 4.

  - Variable: Presence of achieving HAI seroconversion for all strains prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.

  - Intercurrent event(s): For participants who discontinue, have major protocol violations, and/or results obtained from out-of-window blood draws.

  - Population-level summary: The proportion of participants achieving HAI seroconversion for all strains (targeted by the study vaccine) and associated 2-sided 95% CIs, by vaccine group, prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.

- The proportion of participants with HAI titers ≥1:40 for all strains before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.

This estimand includes the following attributes:

- Treatment: 1-Visit schedules or 2-visit schedules with modRNA, licensed QIV, and/or placebo or their combinations as listed in Table 2.
- Population: Evaluable immunogenicity population as defined in Section 4.
- Variable: Presence of participants with HAI titers ≥1:40 for all strains before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Intercurrent event(s): For participants who discontinue, have major protocol violations, and/or results obtained from out-of-window blood draws.
- Population-level summary: The proportion of participants with HAI titers ≥1:40 for all strains and associated 2-sided 95% CIs, by vaccine group, before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.

2.2.2.2.2. Participants From 18 Through 64 Years of Age

In participants from 18 through 64 years of age, the estimands will be defined and analyzed similarly as above. The time points will be adjusted to 1, 4, and 8 weeks after receipt of vaccination. The baseline will be before vaccination.

2.2.3. Tertiary/Exploratory Estimands

CCI [redacted]

[redacted]

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[redacted]

CCI

[redacted]

2.3. Study Design

2.3.1. Overall Design

This is a Phase 1/2 randomized, single-blinded (sponsor-unblinded) study to evaluate the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals from 18 through 85 years of age.

In participants from 65 through 85 years of age:

Participants will be randomized to and will be blinded to which 1-visit or 2-visit vaccination schedules they will receive:

2-Visit Schedules

- 2 Doses of qIRV encoding 2 A strains and 2 B strains at a dose level of CCI , administered 21 days apart
- 2 Doses of licensed QIV, administered 21 days apart (as a control group)
- A dose of licensed QIV following by a dose of bIRV encoding 2 A strains at a dose level of either CCI , administered 21 days apart

1-Visit Schedules

- A dose of licensed QIV administered concurrently in the opposite arm with bIRV encoding 2 A strains at a dose level of either CCI
- A dose of bIRV encoding 2 A strains at a dose level of CCI administered concurrently in the opposite arm with bIRV-encoding 2 B strains at a dose level of CCI
- A dose of qIRV encoding 2 A strains and 2 B strains at the following dose level combinations:
  - CCI
  -
  -
- A dose of licensed QIV (as a control group)

Substudy B enrollment will be separated into an initial and expanded enrollment. Depending on the availability of study intervention and operational prioritization, groups in Substudy B may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any 1 time.

During initial enrollment, each group (vaccine formulation/dose level, or control) will comprise 15 participants. Hence, Substudy B initial enrollment will comprise approximately 165 participants.

Substudy B expanded enrollment will comprise group(s) of 120 participants following the vaccination schedule(s) as selected by the sponsor's IRC from initial enrollment. If deemed acceptable, an additional 120 participants will be enrolled in that group (expanded enrollment). Additionally,

- Expanded-enrollment groups may also be included that comprise only the first dose from 2-visit–schedule initial-enrollment groups, eg, 1 dose of qIRV at a dose level of CCI [redacted].
- A control group of 120 participants will be enrolled during expanded enrollment who will receive a dose of licensed QIV followed by placebo, administered 21 days apart.

In participants from 18 through 64 years of age:

Participants will be randomized to and will be blinded to two 1-visit schedules:

- A dose of qIRV encoding 2 A strains and 2 B strains at a dose level of CCI [redacted].
- A dose of qIRV encoding 2 A strains and 2 B strains at a dose level of CCI [redacted].

Two hundred forty participants will be randomized in a 1:1 ratio to 1 of the 2 above vaccination groups.

Therefore, Substudy B will consist of approximately 645 to 1725 participants, depending on the number of groups selected to progress to expanded enrollment.

Dose levels detailed above are summarized in Table 2.

Table 2. modRNA Vaccine Doses Encoding HA for Each Strain

Initial Enrollment (Participants From 65 Through 85 Years of Age) (N = 15 per group)						Expanded Enrollment (N = 120 per group)	
Vaccination 1		Vaccination 2				Vaccination 1	Vaccination 2
Right Deltoid	Left Deltoid	Right Deltoid	Left Deltoid			Right Deltoid	Left Deltoid
qIRV CCI 2 x A, 2 x B CCI		qIRV CCI 2 x A, 2 x B CCI		→ [a]	**Participants from 18 through 64 years of age**	qIRV CCI 2 x A, 2 x B CCI	
Licensed QIV		bIRV CCI 2 x A CCI				qIRV CCI 2 x A, 2 x B CCI	
Licensed QIV		bIRV CCI 2 x A CCI			**Participants from 65 through 85 years of age**	Licensed QIV[b]	Placebo
Licensed QIV		Licensed QIV				Other vaccine group(s) as selected by the sponsor's IRC from initial enrollment for expanded enrollment. Expanded-enrollment groups may also be included that comprise only the first dose from 2-visit–schedule initial enrollment groups.	
bIRV CCI 2 x A CCI	Licensed QIV						
bIRV CCI 2 x A CCI	Licensed QIV						
qIRV CCI 2 x A, 2 x B CCI							
Licensed QIV							
bIRV CCI 2 x B CCI	bIRV CCI 2 x A CCI						
qIRV CCI 2 x A CCI 2 x B CCI							
qIRV CCI 2 x A CCI 2 x B CCI							

a. Safety and immunogenicity data accumulated at least 1 week following the last vaccination in each group will be reviewed and, if the data are deemed acceptable, an additional 120 participants will be enrolled in that group (expanded enrollment).

b. At the discretion of the sponsor's IRC, a control group of 120 participants may be enrolled during the expanded enrollment who will receive a dose of licensed QIV followed by placebo, administered 21 days apart.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

All participants will be asked to monitor and record local reactions, systemic events, and use of antipyretic medication for 7 days from the day of administration of each vaccination. These prospectively self-collected occurrences of local reactions and systemic events will be graded. The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[2] Below are the primary safety endpoints for local reactions and systemic events:

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after each vaccination in each vaccine group.

- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) within 7 days after each vaccination in each vaccine group.

For all participants randomized and receiving at least 1 dose of study intervention, below are the primary safety endpoints for AEs and SAEs:

- AEs from the first vaccination through 4 weeks after the last vaccination.

- SAEs from the first vaccination through 6 months after the last vaccination.

3.1.1.1. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. Local reactions will be assessed at the injection site on the right arm only.

If a local reaction persists beyond the end of the reactogenicity e-diary period following each vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 3. 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 3.

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

Presence or Absence

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

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

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

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

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

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

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

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

Severity and Maximum Severity

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

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

Duration (First to Last Day Reported)

For participants experiencing any local reactions (or those with a derived reaction as described in Table 4), the maximum duration (last day of reaction - first day of reaction + 1) will be derived for each study vaccination group. 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

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.

In summary, the following variables will be derived for local reactions:

1. Presence or absence of each local reaction on each day (Day 1-7) after vaccination.
2. Presence or absence of each local reaction on "any day (Day 1-7)" after vaccination.
3. Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.
4. Presence or absence of any local reaction on "any day (Day 1-7)" after vaccination.
5. Duration of each local reaction after vaccination.
6. Onset day of each local reaction after vaccination.
7. Onset day of any local reaction after vaccination.

3.1.1.2. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5. 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.

Table 5. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of event, severity level, duration, and onset day. The variables associated with the systemic events will be computed similarly to the way local reactions are computed (see Section 3.1.1.1).

3.1.1.3. Fever

Oral temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place.

Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Temperatures <35.0°C and >42.0°C will be excluded from the analysis. Fever will be grouped into ranges for the analysis according to Table 6.

Table 6. 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 ≥38.0°C (≥100.4°F).

3.1.1.4. Use of Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 through Day 7).

For the use of antipyretic medication from Day 1 through Day 7 after each dose, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable:

- Presence (yes or no) of use of antipyretic medication on each day (Day 1-7).
- Presence (yes or no) of use of antipyretic medication on any day (Day 1-7).
- Duration (first to last day reported) of use of antipyretic medication.
- Onset day of use of antipyretic medication.

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.5. Adverse Events

The time period for actively eliciting and collecting AEs and SAEs, "the 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 (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 206 (4-week follow-up visit) for Substudy B. Additionally, for Substudy B, any AEs occurring up to 48 hours after the blood draws at Visits 206 and 207 must be recorded on the CRF.

Acute reactions within the first 30 minutes after each vaccination will be assessed and documented in the AE CRF. Such acute reactions, if any, are defined as immediate AEs.

SAEs will be collected from the time the participant provides informed consent to approximately 6 months after the participant's last study vaccination (Visit 208 for Substudy B).

Adverse events of special interest include:

- A confirmed diagnosis of influenza;
- A confirmed diagnosis of myocarditis or pericarditis.

3.1.1.6. Chemistry Laboratory Parameters

Troponin I laboratory parameters will be collected. The primary endpoints include abnormal troponin values 2 days after the last vaccination.

The troponin I tests will be performed at screening and Visits 201 (Day 1) and 204 (2 to 4 days after the last vaccination).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

3.1.1.7. 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 but not limited to the following:

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

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

In participants complying with the key protocol criteria (evaluable participants), the endpoints include:

- HAI titers for each strain targeted by the study vaccine.

3.3. Tertiary/Exploratory Endpoints

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3.4. Baseline Variables

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

3.4.1. Demographics, Medical History, and Physical Examination

The demographic variables are age at Vaccination 1 (in years), sex (male or female), race (Black or African American, American Indian, or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White), and ethnicity (Hispanic/Latino[a] or of Spanish origin, non-Hispanic/non-Latino[a] or of Spanish origin). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age (in years) will be derived based on the participant's birthday and the date the participant receives Vaccination 1. For example, if the vaccination day is 1 day before the participant's 66th birthday, the participant is considered to be 65 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 obtained from all participants at their screening visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF. Medical history will be categorized according to MedDRA.

A physical examination will be performed at the screening visit but is not mandated for Vaccination 1. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

3.4.2. E-Diary Completion

For all participants, an e-diary will be considered transmitted if any data for local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study. Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination.

- Receipt of any mRNA-platform SARS-CoV-2 vaccine within 28 days before and 28 days after any study vaccination that contains modRNA.
- Receipt of any other (nonstudy) seasonal influenza vaccine is prohibited from enrollment through Visit 207 (8-week follow-up visit).
- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study is prohibited.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through 28 days after administration of the last study intervention.
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

3.5. Safety Endpoints

Local reaction, systemic event, AE, and SAE assessments, abnormal troponin I laboratory tests, and assessment of ECG abnormalities are described above in the Primary Safety Endpoints section (Section 3.1.1).

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. The populations are defined below:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to study intervention	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All participants who: • Are eligible (have signed informed consent and met all inclusion/exclusion criteria); • Receive the vaccines according to the group to which they were randomized (ie, 1-visit or 2-visit schedules);

Population	Description
	• Have blood drawn for assay testing within the specified time frame (26-35 days) after the last vaccination (1-visit or 2-visit schedules); • Have at least 1 valid and determinate assay result at the 4-week follow-up visit (26-35 days) following the last vaccination (1-visit or 2-visit schedules); • Have no major protocol violations.
mITT	All randomized participants who: • Receive the study intervention(s) (1-visit or 2-visit schedules); • Have at least 1 valid and determinate assay result after the last vaccination (1-visit or 2-visit schedules). The immunogenicity results based on the mITT population will be summarized for immunogenicity endpoints if there is a ≥10% difference between the mITT population and the evaluable immunogenicity population.
Vaccination 1 safety	All participants who received Vaccination 1 from 2-visit schedule.
Vaccination 2 safety	All participants who received Vaccination 2 from 2-visit schedule.
Safety	All participants who received the study intervention.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety populations. Participants will be summarized by vaccine 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 in sample size between the mITT population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses in the study.

5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for the continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for the categorical variables are the proportion (%) and the numerator (n) and the denominator (N) used in the calculation of the proportion.

All safety and immunogenicity summaries will be presented by vaccine group unless otherwise explicitly stated. The data from initial and expanded enrollments will be analyzed separately. The same analyses will be repeated for expanded enrollment as those in initial enrollment.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for the 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 the binary endpoints of each group will be computed using the F distribution (Clopper and Pearson method).[3] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[4]

5.2.1.1. Safety Data

All safety analyses will be performed on the safety populations.

For safety data, as defined in Section 3.1.1, the exact 2-sided 95% CIs using the Clopper and Pearson method will be provided by vaccine group for all primary safety endpoints and for proportions of participants reporting local reactions, systemic events, AEs (including immediate AEs), SAEs, abnormal troponin I values, and new ECG abnormalities. The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.

5.2.1.2. Immunogenicity Data

The proportion of participants achieving HAI seroconversion at each time point after each vaccination, and the proportion of participants with HAI titers ≥1:40 before each vaccination and at each time point after each vaccination, and associated 2-sided Clopper-Pearson 95% CIs will be provided by vaccine group for each strain, all strains, and each heterologous strain.

5.2.2. Analyses for Continuous Endpoints

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

5.2.2.1. Geometric Means

The geometric mean will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits. When multiple records are available, the average of the records will be calculated as the value to be analyzed. The records from the same run will be paired and analyzed. For example, the same-run baseline record will be paired with postvaccination records to calculate the seroconversions.

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. When prevaccination assay results are lower than the LLOQ and the postvaccination results are greater than or equal to the LLOQ, the prevaccination assay results will be set to LLOQ for 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 Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

For example, HAI GMFRs will be calculated as the mean difference of logarithmically transformed assay results from before vaccination to each time point after vaccination, and associated 2-sided 95% CIs, will be provided by vaccine group.

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 Student's 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.

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5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Completely missing reactogenicity e-diary data will not be imputed; missing AE dates, missing laboratory test values, and missing ECG values will be handled according to the Pfizer safety rules.

5.3.1.1. Reactogenicity Data

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

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of 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 3.1.1.1 and Section 3.1.1.2.

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, with the exception of that mentioned for GMFR in Section 5.2.2.2. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

Values that are designated as serum QNS, IND, or "not done" will be set to missing. No imputation will be done for these missing values.

LLOQ results for each assay used in this study will be included in the analysis specification once they are available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days following each vaccination (Section 3.1.1.1).
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules (Section 4).
- Analysis time point: Day 1 through Day 7 after each vaccination. Refer to Section 3.1.1.1 for maximum severity.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after each vaccination will be excluded from the analysis at that particular vaccination. For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- Reporting results: The proportion, the numerator (n) and denominator (N) used for the calculation of the proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented, by vaccine group, for the following variables:
  - Presence or absence of each local reaction on each day (Day 1-7) after vaccination.
  - Presence or absence of each local reaction on “any day (Day 1-7)” after vaccination.
  - Presence or absence of any local reaction on “any day (Day 1-7)” after vaccination.
  - Maximum severity of each local reaction on “any day (Day 1-7)” after vaccination.
- The n, mean, standard deviation, median, minimum, and maximum will be presented by vaccine group, for the following variables:
  - Duration of each local reaction after vaccination.

- Onset day of each local reaction after vaccination.
- Onset day of any local reaction after vaccination.

Figures:

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

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following each vaccination (Section 3.1.1.2).
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules (Section 4).
- Analysis time point: Day 1 through Day 7 after each vaccination. Refer to Section 3.1.1.1 for maximum severity.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that particular vaccination. For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- Reporting results: Descriptive statistics for each systemic event after each dose will be presented by maximum severity and cumulatively across severity levels by vaccine group. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs.

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

The use of antipyretic medication (see Section 3.1.1.4) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

Figures:

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

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs from the first vaccination through 4 weeks after the last vaccination.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Day 1 from the first vaccination through 4 weeks after the last vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Reporting results: The number of participants with AEs from the first vaccination though 4 weeks after the last vaccination (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented for any AE, immediate AEs, severe AEs, related AEs, and AEs leading to withdrawal for each SOC, and each PT within each SOC, by vaccine group.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from the first vaccination through 6 months after the last vaccination.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Day 1 from the first vaccination through 6 months after the last vaccination.
- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

- Reporting results: The number of participants with SAEs from the first vaccination though 6 months after the last vaccination (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented for each SOC, and each PT within each SOC, by vaccine group.

6.1.1.5. Chemistry Laboratory Parameters

6.1.1.5.1. Abnormal Troponin I Laboratory Values

6.1.1.5.1.1. Main Analysis

- Estimand: The percentage of participants with abnormal troponin I values 2 days after the last vaccination.

- Estimand strategy: Treatment policy (Section 2.2.1).

- Analysis set: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules (Section 4).

- Analysis time point: 2 Days after the last vaccination.

- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing abnormal test values will be handled according to Pfizer safety rules.

- Reporting results: The number of participants with abnormal troponin I values 2 days after the last vaccination (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented for each test by vaccine group.

6.1.1.6. Electrocardiograms

6.1.1.6.1. Main Analysis

- Estimand: The percentage of participants with new ECG abnormalities 2 days after the last vaccination.

- Estimand strategy: Treatment policy (Section 2.2.1).

- Analysis set: Safety population for 1-visit schedules and Vaccination 1 safety population or Vaccination 2 safety population for 2-visit schedules (Section 4).

- Analysis time point: 2 Days after the last vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing ECG values will be handled according to Pfizer safety rules.
- Reporting results: The number of participants with new ECG abnormalities (as defined in Section 3.1.1.7) 2 days after the last vaccination (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented by vaccine group.

6.2. Secondary Endpoints

6.2.1. HAI Titers for Each Strain Targeted by the Study Vaccine

6.2.1.1. Participants From 65 Through 85 Years of Age

6.2.1.1.1. The Analyses in Sections 6.2.1.1.1 to 6.2.1.1.4 are for Participants From 65 Through 85 Years of Age HAI GMTs at Each Scheduled Visit

6.2.1.1.1.1. Main Analysis

- Estimand: HAI GMTs before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Day 1 before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: HAI GMTs (Section 5.2.2.1) and associated 2-sided 95% CIs will be provided by vaccine group and strain(s) before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.

Figures:

- Empirical RCDCs (Section 5.2.2.4) will be provided for HAI GMTs by vaccine group and strain(s) before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.

- HAI GMTs and associated 95% CIs will be plotted by vaccine group and strain(s) before Vaccination 1, prior to Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after the last vaccination.

6.2.1.1.2. HAI Geometric Mean Fold Rises After Receipt of Vaccination 1

6.2.1.1.2.1. Main Analysis

- Estimand: HAI GMFRs from before Vaccination 1 to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after receipt of the last vaccination.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Day 1 before Vaccination 1 (baseline for calculation) to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after receipt of the last vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: HAI GMFRs (Section 5.2.2.2) from before Vaccination 1 to prior to Vaccination 2 (Day 21, if applicable) and to 1, 4, and 8 weeks after receipt of the last vaccination, and associated 2-sided 95% CIs, will be provided by vaccine group and strain(s).

6.2.1.1.3. The Proportion of Participants Achieving HAI Seroconversion for Each Strain at Each Time Point After Receipt of Vaccination 1

6.2.1.1.3.1. Main Analysis

- Estimand: The proportion of participants achieving HAI seroconversion for each strain prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

- Reporting results: The proportion of participants achieving HAI seroconversion for each strain and associated 2-sided Clopper-Pearson 95% CIs will be provided by vaccine group prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.

Figures:

Bar charts with the numbers, proportions, and associated 95% CIs of participants achieving HAI seroconversion for each strain prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be plotted by vaccine group.

6.2.1.1.4. The Proportion of Participants With HAI Titers ≥1:40 for Each Strain Before Vaccination 1 and at Each Time Point After Vaccination 1

6.2.1.1.4.1. Main Analysis

- Estimand: The proportion of participants with HAI titers ≥1:40 for each strain before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.

- Estimand strategy: Hypothetical strategies (Section 2.2.2).

- Analysis set: Evaluable immunogenicity population (Section 4).

- Analysis time points: Day 1 before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.

- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

- Reporting results: The proportion of participants with HAI titers ≥1:40 for each strain before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be provided by vaccine group.

6.2.1.2. Participants From 18 Through 64 Years of Age

For participants from 18 through 64 years of age, the analyses in Sections 6.2.1.1.1 to 6.2.1.1.4 will be applied similarly as above. The time points will be adjusted to 1, 4, and 8 weeks after receipt of vaccination. The baseline will be before vaccination.

6.2.2. HAI Titers for Each Strain Targeted by the Study Vaccine for All Strains

6.2.2.1. Participants From 65 Through 85 Years of Age

The analyses in Sections 6.2.2.1.1 to 6.2.2.1.2 are for participants from 65 through 85 years of age.

6.2.2.1.1. The Proportion of Participants Achieving HAI Seroconversion for All Strains at Each Time Point After Receipt of Vaccination 1

6.2.2.1.1.1. Main Analysis

- Estimand: The proportion of participants achieving HAI seroconversion for all strains prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: The proportion of participants achieving HAI seroconversion for all strains (targeted by the study vaccine) prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be presented for participants who received at least 1 dose of qIRV or licensed QIV, by vaccine group.

Figures:

Bar charts with the numbers, proportions, and associated 95% CIs of participants achieving HAI seroconversion for all strains prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be plotted by vaccine group.

6.2.2.1.2. The Proportion of Participants With HAI Titers ≥1:40 for All Strains Before Vaccination 1 to Each Time Point After Receipt of Vaccination 1

6.2.2.1.2.1. Main Analysis

- Estimand: The proportion of participants with HAI titers ≥1:40 for all strains before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Day 1 before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: The proportion of participants with HAI titers ≥1:40 for all strains before Vaccination 1, before Vaccination 2 (Day 21, if applicable), and at 1, 4, and 8 weeks after receipt of the last vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be provided for participants who received at least 1 dose of qIRV or licensed QIV, by vaccine group.

6.2.2.2. Participants From 18 Through 64 Years of Age

For participants from 18 through 64 years of age, the analyses in Sections 6.2.2.1.1 to Section 6.2.2.1.2will be applied similarly as above. The time points will be adjusted to 1, 4, and 8 weeks after receipt of vaccination. The baseline will be before vaccination.

6.3. Tertiary/Exploratory Endpoints

CCI [redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

6.4. Subset Analyses

Not applicable.

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 1, sex, race, and ethnicity) will be generated by vaccine group based on the safety populations. The summary will be done by age group and overall, as appropriate.

The number and proportion of participants with at least 1 medical history PT, arranged by SOC, will be tabulated by vaccine group based on the safety populations. The summary will be done by age group and overall, as appropriate.

Participant data listings for demography and baseline characteristics data will also be generated.

Each reported medical history term will be mapped to an SOC and PT according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group based on the safety populations.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions, the 7 systemic events, fever, and the use of antipyretic medications) are available. If any of the items in the e-diary are missing on a specific day, the e-diary will not be transmitted, and the e-diary data will be missing for all items on that day. There is no possibility of partial filling of 1-day e-diary data. The e-diary completion (or transmission) rate will be provided after each vaccination on "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," and "Day 7". The denominator will be the total number of participants who received the vaccination, and the numerator will be the total number of participants with e-diary data transmitted on a given day. Additional e-diary compliance parameters for each vaccination will be derived as follows for presence or absence of each local reaction on each day (Day 1-7) after vaccination:

1. E-diaries are completed for at least 1 day. The numerator is the number of participants who completed (transmitted) the e-diary on any day, and the denominator is the total number of participants who received a vaccination.

2. E-diaries are completed for at least 2 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 2 days, and the denominator is the total number of participants who received a vaccination.

3. E-diaries are completed for at least 3 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 3 days, and the denominator is the total number of participants who received a vaccination.

4. E-diaries are completed for at least 4 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 4 days, and the denominator is the total number of participants who received a vaccination.

5. E-diaries are completed for at least 5 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 5 days, and the denominator is the total number of participants who received a vaccination.

6. E-diaries are completed for at least 6 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 6 days, and the denominator is the total number of participants who received a vaccination.

7. E-diaries are completed for 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.

The number and proportion of participants with e-diary data not transmitted, transmitted by day (Day 1-7), and transmitted all 7 days will be summarized by vaccine group.

6.5.2.2. Participant Disposition

The number and proportion of assigned participants will be included in the participant disposition summary. In addition, participants who completed each follow-up visit and withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by vaccine group. The reasons for withdrawal will be those as specified in the database. Additionally, participants who missed at least 1 study procedure but continued in the study for safety follow-up will be summarized. The summary will be done by age group and overall, as appropriate.

Participants excluded from the evaluable immunogenicity population and mITT population will also be summarized with reasons for exclusion.

The number and proportion of participants assigned, vaccinated, and who had blood drawn within the protocol-specified time frame and outside the specified window for all participants will be tabulated by vaccine group.

Participant data listings of participants who withdrew during the study will be generated. Also, data listings for participants excluded from the evaluable immunogenicity population and mITT population will be generated.

The protocol violation listings from Vaccination 1 will be generated. In addition, participants who do not receive Vaccination 1 as assigned will be listed.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated by vaccine group. The denominator for the percentages is the number of participants randomized in vaccine groups.

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

A listing of participants showing the randomized vaccine and the vaccine actually received will be presented separately for each vaccine group as described in Section 2.3.1.

6.5.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification/WHO Drug Dictionary, as appropriate. All prohibited vaccines and medications, along with the windows listed in Section 3.4.3, will be listed. The number and percentage of participants receiving each concomitant vaccine after Vaccination 1 will be tabulated by vaccine group. The safety populations will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines. The summary will be done by age group and overall, as appropriate.

6.6. Safety Summaries and Analyses

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

The urine pregnancy results for participants from 18 through 64 years of age might be listed as appropriate.

6.6.1. Vital Signs

A descriptive summary, including weight, height, body temperature, pulse rate, and seated blood pressure, based on the safety populations will be provided in accordance with the Pfizer reporting standards, and listings may be generated.

6.6.2. Physical Examination

Not applicable.

7. INTERIM ANALYSES

7.1. Introduction

This study will use an IRC. 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 phase. 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.

If serology data are available but with limited 4-week serology data after vaccination, the mITT population, not the evaluable immunogenicity population, might be used for any analyses to support IRC review.

The responsibilities of the IRC will include at a minimum:

- Review of safety data in the case of a stopping rule being met.
- Review of safety and immunogenicity data accumulated at least 1 week following the last vaccination in each group during initial enrollment.

8. REFERENCES

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3. 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
ATC	Anatomic Therapeutic Chemical
bIRV	bivalent influenza modRNA vaccine
BLQ	below the level of quantitation
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
FDA	Food and Drug Administration (United States)
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
ICD	informed consent document
IND	indeterminate
IRC	internal review committee
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
LOD	limit of detection
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
PBMC	peripheral blood mononuclear cell
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

Abbreviation	Term
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
WHO	World Health Organization

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Signed By:	Date(GMT)	Signing Capacity
PPD	27-Jul-2022 18 02 34	Final Approval

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