Protocol C4781001 – Substudy A

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

Statistical Analysis Plan
(SAP)

Version: 4

Date: 03 Jun 2022

[redacted]

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CCI

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
4/ 03 Jun 2022	Final Protocol Amendment 4, 08 Feb 2022	Removed expanded enrollment	Changed Section 2.3
		CCI [redacted]	CCI [redacted]
		Made changes in cell-mediated immune responses	Changed Section 2.2.3.4 and Section 6.3.4
		Revised text describing ECG endpoints	Changed Section 3.5 and Section 6.6
		Updated to new SAP template	Added Section 2.2.1; changed Section 2.2, Section 6.1, Section 6.2, and Section 6.3
		Removed MN objective and estimands	Removed Sections 2.1.6.3 and 6.3.2 in SAP v3
		Clarified the Vaccination 2 evaluable population definition and added the safety population	Changed Section 4
		Added details of GMR analyses	Changed Section 5.2.2.3
		Updated the RCDC step function	Changed Section 5.2.2.4
		Removed 'for qIRV and QIV vaccine groups' in sections 6.3.1.1 – 6.3.1.4' to match those in section 2.2.3.1.	Changed Sections 6.3.1.1 - 6.3.1.4
3/ 31 Dec 2021	Final Protocol Amendment 2, 04 Dec 2021	Objectives, endpoints, and estimands were changed after the addition of Vaccination 2	Changed Sections 2.1.3, 2.1.4, 2.1.5, and 2.1.6
		Analysis populations were changed	Changed Section 4
		Study design was changed	Changed Section 2.2.1
		Analyses were changed following Vaccination 2	Changed Sections 5 and 6
		Imputation rule was changed related to GMFR	Changed Sections 5.2.2.2 and 5.3.2
2/ 17 Sep 2021	Final Protocol Amendment 1, 14 Aug 2021	Age of study population changed to 65 to 85 years of age	Changed age range in Sections 2.1.1, 2.1.2, 2.1.3, and 2.2.1
		Objectives, estimands, and endpoints updated	Changed objectives, estimands, and endpoints in Sections 2.1, 3.1.1, 3.2.1, and 3.3.1 Changed time points in Section 6.1.1.4 Added laboratory and ECG endpoints in Section 2.1.4 Added laboratory endpoints in Section 3.1.1.6 Added an ECG endpoint in Section 3.1.1.7

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
		Removal of Phase 2	Changed Sections 2, 2.1.4, 2.2.1, and 3.1.1 to remove Phase 2
		Schema updated to reflect design changes	Changed Section 2.2.1
		Change in number of participants	Changed Section 2.2.1
		Removal of data monitoring committee	Changed Section 7
		Updated statistical methods text	Changed Sections 5 and 6
		Addition of prohibited modRNA-platform SARS-CoV-2 vaccine within 60 days before and 60 days after vaccination	Changed Section 3.4.3
		Added tertiary objectives/estimands, and endpoints that are not included in protocol amendment 1	Changes made in Sections 2.1.3, 2.1.6.5, 2.1.6.6, 6.3.4, and 6.3.5
1/ 09 Jul 2021	Final Protocol, 27 May 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4781001 – Substudy A. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

The MN objective and estimands have been removed. MN as a replacement option for HAI, if clear HAI results are not obtainable, has been removed.

2.2. Study Objectives, Endpoints, and Estimands

Substudy A (Phase 1)

Type	Objectives	Estimands	Endpoints
Primary safety	To describe the safety and tolerability of mIRV, bIRV, and qIRV in adults 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 Vaccinations 1 and 2 • Systemic events for up to 7 days following Vaccinations 1 and 2 • AEs 4 weeks after Vaccinations 1 and 2 • SAEs from the first vaccination to 6 months 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
		The percentage of participants with: • Abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 2 days and 1 week after Vaccination 1	Hematology and chemistry laboratory parameters
		The percentage of participants with: • New ECG abnormalities 2 days and 1 week after Vaccination 1	ECG abnormalities consistent with probable or possible myocarditis or pericarditis
Secondary immune responses	To describe the immune responses elicited by mIRV, bIRV, and qIRV in adults 65 to 85 years of age	In participants complying with the key protocol criteria (evaluable participants) at 1, 4, and 8 weeks after receipt of Vaccination 1: • HAI GMTs at 1, 4, and 8 weeks after receipt of Vaccination 1 • HAI GMFR from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1 • The proportion of participants achieving HAI seroconversion for each strain at 1, 4, and 8 weeks after receipt of Vaccination 1	HAI titers for each strain targeted by the study vaccine

Type	Objectives	Estimands	Endpoints
		• The proportion of participants with HAI titers ≥1:40 for each strain before Vaccination 1 and at 1, 4, and 8 weeks after receipt of Vaccination 1	
		In participants having received qIRV or licensed QIV at Visit 1, complying with the key protocol criteria (evaluable participants) at 1, 4, and 8 weeks after receipt of Vaccination 1: • The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of Vaccination 1 • The proportion of participants with HAI titers ≥1:40 for all strains before vaccination to 1, 4, and 8 weeks after receipt of Vaccination 1 • GMR of HAI titers for each strain in qIRV recipients compared to comparator recipients 4 weeks after Vaccination 1 • The difference in percentage of participants achieving seroconversion for each strain at 4 weeks after Vaccination 1 in qIRV recipients compared to comparator recipients	HAI titers for each strain targeted by the study vaccine
CCI [redacted]	[redacted]	[redacted]	[redacted]

Type	Objectives	Estimands	Endpoints
		CCI	

Type	Objectives	Estimands	Endpoints
		[redacted]	
		[redacted]	[redacted]

Type	Objectives	Estimands	Endpoints
		CCI [redacted]	
[redacted]	[redacted]	[redacted]	[redacted]

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 vaccine actually received.

In participants receiving at least 1 dose of study intervention:

- The percentage of participants reporting prompted local reactions up to 7 days following Vaccinations 1 and 2.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV; 2 different vaccinations at 2 separate vaccination visits where the study intervention received at Vaccination 2 was switched based on the study intervention received at Vaccination 1, as described in Section 2.3.
  - Population: Participants 65 through 85 years of age who received Vaccination 1 or Vaccination 2 as the study intervention.
  - Variable: Presence/absence of prespecified local reactions up to 7 days after Vaccinations 1 and 2.
  - Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
  - Population-level summary: Percentage and associated exact 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 Vaccinations 1 and 2.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV; 2 different vaccinations at 2 separate vaccination visits where the study intervention received at Vaccination 2 was switched based on the study intervention received at Vaccination 1, as described in Section 2.3.
  - Population: Participants 65 through 85 years of age who received Vaccination 1 or Vaccination 2 as the study intervention.

- Variable: Presence/absence of prespecified systemic events up to 7 days after Vaccinations 1 and 2.
- Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
- Population-level summary: Percentage and associated exact 2-sided 95% CI of participants reporting systemic events in each vaccine group.

- The percentage of participants reporting AEs from vaccination through 4 weeks after Vaccinations 1 and 2.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV; 2 different vaccinations at 2 separate vaccination visits where the study intervention received at Vaccination 2 was switched based on the study intervention received at Vaccination 1, as described in Section 2.3.
  - Population: Participants 65 through 85 years of age who received Vaccination 1, Vaccination 2, or both as the study intervention.
  - Variable: Presence of AEs through 4 weeks after Vaccinations 1 and 2.
  - Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
  - Population-level summary: Percentage and associated exact 2-sided 95% CI of participants reporting AEs 4 weeks after Vaccinations 1 and 2 in each vaccine group.

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

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV; 2 different vaccinations at 2 separate vaccination visits where the study intervention received at Vaccination 2 was switched based on the study intervention received at Vaccination 1, as described in Section 2.3.

- Population: Participants 65 through 85 years of age who received Vaccination 1, Vaccination 2, or both as the study intervention.
- Variable: Presence of SAEs through 6 months after the last vaccination.
- Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
- Population-level summary: Percentage and associated exact 2-sided 95% CI of participants reporting SAEs through 6 months after the last vaccination in each vaccine group.

- The percentage of participants with abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.
  - Population: Participants 65 through 85 years of age who received Vaccination 1 as the study intervention.
  - Variable: Presence of abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1.
  - Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
  - Population-level summary: Percentage and associated exact 2-sided 95% CI of participants with abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1 in each vaccine group.

- The percentage of participants with grading shifts in hematology and chemistry laboratory assessments from baseline to 2 days and 1 week after Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.

- Population: Participants 65 through 85 years of age who received Vaccination 1 as the study intervention.
- Variable: Grading of hematology and chemistry laboratory values at baseline and 2 days and 1 week after Vaccination 1.
- Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
- Population-level summary: Percentage and associated exact 2-sided 95% CI of participants with grading shifts from baseline to 2 days and 1 week after Vaccination 1 in each vaccine group.

- The percentage of participants with new ECG abnormalities 2 days and 1 week after Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.
  - Population: Participants 65 through 85 years of age who received Vaccination 1 as the study intervention.
  - Variable: Presence of ECG abnormalities (as defined in Section 3.1.1.7) 2 days and 1 week after Vaccination 1.
  - Intercurrent event(s): All data after an intercurrent event (receiving prohibited vaccine and concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of study, etc.), if collected, will be included.
  - Population-level summary: Percentage and associated exact 2-sided 95% CI of participants with new ECG abnormalities 2 days and 1 week after Vaccination 1 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 of ≥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. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed.

2.2.2.1. Secondary Immunogenicity Estimands, HAI Titers for Each Strain Targeted by Vaccination 1

- HAI GMTs at 1, 4, and 8 weeks after receipt of Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.
  - Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
  - Variable: HAI GMTs on Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.
  - Intercurrent event(s): The following intercurrent events could impact the interpretation or the measurement of the immune response:
    - Not receiving Vaccination 1 as randomized.
    - Not meeting the study inclusion/exclusion criteria before Vaccination 1.
    - Having major protocol violations before Vaccination 2 (received prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).
    - Blood was taken outside of the defined window of 4 weeks, ie, 26 to 35 days, after Vaccination 1.
  - All data after intercurrent events, if collected, will be excluded. The intercurrent events will be referred to as Vaccination 1 intercurrent events.
  - Population-level summary: HAI GMTs and associated 2-sided 95% CI for each strain targeted by the study intervention (by formulation/dose level or control) from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1.

- HAI GMFRs from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1.

This estimand includes the following attributes:

- Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.
- Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
- Variable: GMFRs from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1.
- Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
- Population-level summary: HAI GMFRs and associated 2-sided 95% CI for each strain targeted by the study intervention (by formulation/dose level or control) from before Vaccination 1 to 1, 4, and 8 weeks after Vaccination 1.

- The proportion of participants achieving HAI seroconversion at 1, 4, and 8 weeks after receipt of Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.
  - Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
  - Variable: Presence of participants achieving HAI seroconversion for each strain at 1, 4, and 8 weeks after Vaccination 1.
  - Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
  - Population-level summary: The proportion of participants achieving HAI seroconversion for each strain and associated exact 2-sided 95% CIs, by vaccine group (formulation/dose level or control), at 1, 4, and 8 weeks after Vaccination 1.

- The proportion of participants with HAI titers ≥1:40 for each strain before Vaccination 1 and at 1, 4, and 8 weeks after Vaccination 1.

  This estimand includes the following attributes:

- Treatment: One vaccination with modRNA in differing formulations/doses or licensed QIV.
- Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
- Variable: Presence of participants with HAI titers ≥1:40 for each strain before Vaccination 1 and at 1, 4, and 8 weeks after Vaccination 1.
- Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
- Population-level summary: The proportion of participants with HAI titers ≥1:40 for each strain and associated exact 2-sided 95% CIs, by vaccine group (formulation/dose level or control), before Vaccination 1 and at 1, 4, and 8 weeks after Vaccination 1.

2.2.2.2. Secondary Immunogenicity Estimands, HAI Titers for Each Strain Targeted by the Study Vaccine (qIRV or Licensed QIV)

- The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with qIRV or licensed QIV.
  - Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
  - Variable: Presence of achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of Vaccination 1.
  - Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
  - Population-level summary: The proportion of participants achieving HAI seroconversion for all strains and associated exact 2-sided 95% CIs, by vaccine group (qIRV or licensed QIV), at 1, 4, and 8 weeks after receipt of Vaccination 1.

- The proportion of participants with HAI titers ≥1:40 for all strains before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with qIRV or licensed QIV.

- Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
- Variable: Presence of participants with HAI titers ≥1:40 for all strains before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1.
- Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
- Population-level summary: The proportion of participants with HAI titers ≥1:40 for all strains and associated exact 2-sided 95% CIs, by vaccine group (qIRV or licensed QIV), before Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.

- GMR of HAI titers for each strain in qIRV recipients compared to comparator recipients 4 weeks after Vaccination 1.

  This estimand includes the following attributes:

  - Treatment: One vaccination with qIRV or licensed QIV. The comparator is licensed QIV.
  - Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.
  - Variable: HAI titers for each strain in qIRV recipients and recipients of comparator licensed QIV 4 weeks after Vaccination 1.
  - Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
  - Population-level summary: GMR of HAI titers and associated 2-sided 95% CIs for each strain in qIRV recipients compared to recipients of comparator licensed QIV 4 weeks after Vaccination 1.

- The difference in percentages of participants achieving seroconversion for each strain at 4 weeks after Vaccination 1 in qIRV recipients compared to comparator recipients.

  This estimand includes the following attributes:

  - Treatment: One vaccination with qIRV or licensed QIV. The comparator is licensed QIV.
  - Population: Participants 65 through 85 years of age, as defined by the inclusion and exclusion criteria.

- Variable: Presence of achieving seroconversion for each strain in qIRV recipients and recipients of licensed QIV comparator at 4 weeks after Vaccination 1.
- Intercurrent event(s): The same as in Section 2.2.2.1 (Vaccination 1 intercurrent events).
- Population-level summary: The differences and associated 2-sided 95% CIs in percentages of participants achieving seroconversion for each strain at 4 weeks after Vaccination 1 in qIRV recipients compared to recipients of licensed QIV comparator.

2.2.3. Tertiary/Exploratory Estimands

CCI [redacted]

[redacted]

[redacted]

CCI

[redacted]

- CCI [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

CCI

CCI

[redacted]

CCI

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CCI

[redacted]

[redacted]

CCI

[redacted]

2.3. Study Design

2.3.1. Overall Design

This is a Phase 1 randomized, observer-blinded (sponsor-unblinded) study to evaluate the safety, tolerability, and immunogenicity of mIRV and bIRV at various dose levels, and qIRV, in individuals 65 to 85 years of age.

Participants will be randomized to receive Vaccination 1 at Visit 1:

- mIRV at a dose level of [redacted] encoding A strain, or QIV,
- mIRV at a dose level of [redacted] encoding B strain, or QIV,

- bIRV in the dose-level combinations shown in Table 2, encoding both A and B strains, or QIV, or
- qIRV encoding HA for 2 A strains and 2 B strains at a dose level of CCI [redacted].

Table 2. Initial Strain and Dose-Level Combinations to Be Used in bIRV During Phase 1

		B Strain	
		CCI	[redacted]
A Strain	CCI		X
	CCI	X	X
	CCI		X

QIV will act as a control. During initial enrollment, each group (vaccine formulation/dose level, or control) receiving mIRV A strain, mIRV B strain, bIRV, and initial qIRV will comprise 15 participants 65 to 85 years of age.

Safety data accumulated at least 1 week following vaccination with mIRV, bIRV, and qIRV will be reviewed and, if deemed acceptable, a further 360 participants can be enrolled and randomized 1:1 to receive either qIRV or QIV. However, based upon preliminary immunogenicity data, the sponsor decided not to expand enrollment in Substudy A. Therefore, approximately 255 participants were enrolled in Substudy A.

The sponsor's IRC judged that the safety profile observed from groups during initial enrollment supports the development of the planned Substudy B. The SAP for Substudy B was prepared separately.

Participants from the initial enrollment period will be unblinded at Visit 5 (8 weeks after Vaccination 1) and licensed QIV will be administered at Visit 5 to participants not having previously received licensed QIV. Additionally, at Visit 5A, participants who previously received licensed QIV at Visit 1 will receive either:

- mIRV at a dose level of CCI encoding A strain (up to 30 participants who previously received QIV at Visit 1), or
- mIRV at a dose level of CCI encoding B strain (up to 30 participants who previously received QIV at Visit 1).

Vaccinations administered at either Visit 5 or Visit 5A will be considered Vaccination 2 for these participants.

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 Vaccinations 1 and 2. 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 Vaccinations 1 and 2 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 Vaccinations 1 and 2 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 vaccination through 4 weeks after Vaccinations 1 and 2.

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

Some participants might have no e-diary data collected from Vaccination 2, and any reactogenicity will be collected in the participant's AE CRF. This part of the data will be considered as the "any reactogenicity within 7 days" analyses for Vaccination 2.

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. If a local reaction persists beyond the end of the reactogenicity e-diary period following Vaccinations 1 and 2, 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 explains the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of each dose.

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

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

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 (Systemic Event Symptoms and Fever)

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 below.

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 through Day 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 4 (4-week follow-up after Vaccination 1) and from Visit 5 (8-week follow-up after Vaccination 1) to Visit 5B (4-week follow-up after Vaccination 2). In addition, any AEs occurring up to 48 hours after the blood draws at Visits 4 and 5B must be recorded on the CRF.

Acute reactions within the first 30 minutes after Vaccinations 1 and 2 will be assessed and documented in the AE CRF. And such acute reactions, if any, are defined as immediate AEs.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent through Visit 6.

Adverse events of special interest include:

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

3.1.1.6. Hematology and Chemistry Laboratory Parameters

Below are the additional primary safety endpoints:

- Abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1.

- Grading shifts in hematology and chemistry laboratory assessments from baseline to 2 days and 1 week after Vaccination 1.

The following safety laboratory tests will be performed at screening and Visits 1, 2, and 3. 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
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase Cardiac troponin I C-reactive protein

The laboratory abnormalities will be graded as shown in Table 7.

Table 7. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (female) - g/dL	10.0 – 10.9	9.0 – 9.9	8.0 – 8.9	<8.0
Hemoglobin (male) - g/dL	11.5 – 12.4	10.0 – 11.4	8.5 – 9.9	<8.5
WBC decrease - cells/mm^3	2500 – 3699	1500 – 2499	1000 – 1499	<1000
WBC increase - cells/mm^3	11,001 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
Eosinophils - cells/mm^3	801 – 1500	1501 – 5000	>5000	Hypereosinophilic
Lymphocytes decrease - cells/mm^3	750 – 899	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1500 – 1699	1000 – 1499	500 – 999	<500
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

Table 7. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Alkaline phosphate - increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	>10 × ULN
Liver function tests - ALT, AST - increase by factor	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10 × ULN
Bilirubin - when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	>1.75 × ULN
Bilirubin - when liver function test is normal - increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	>3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell

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

All scheduled 12-lead ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. The ECGs should be obtained prior to blood collection, blood pressure, and pulse rate. ECGs will be performed in triplicate.

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 atrioventricular block, new bundle branch block
- Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis

The percentage of participants with new ECG abnormalities 2 days and 1 week after Vaccination 1 will be summarized in each vaccine group.

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

CCI [redacted]

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), ethnicity (Hispanic or Latino[a] or of Spanish origin, not Hispanic or Latino[a] or of Spanish origin), 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.

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 first visit (Visit 1) 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 may be performed prior to Vaccination 1 but is not required for all participants. 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 60 days before and 60 days after study vaccination.
- Receipt of any other (nonstudy) seasonal influenza vaccine at any time during study participation is prohibited.
- 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, clinical safety laboratory assessments of hematology and chemistry, and assessment of ECG abnormalities have been described above in the primary safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per 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.
Vaccination 1 evaluable	All participants who: • Are eligible (have signed informed consent and met all inclusion/exclusion criteria before Vaccination 1); • Receive the study intervention (Vaccination 1) to which they were randomized; • Have blood drawn for assay testing within the specified time frame (26-35 days) after Vaccination 1; • Have at least 1 valid and determinate assay result at the 4-week (26-35 days after Visit 1) post–Vaccination 1 visit; • Have no major protocol deviations before Vaccination 2.

Population	Description
Vaccination 2 evaluable	All participants who: • Are eligible (have signed informed consent and met all inclusion/exclusion criteria before Vaccination 2); • Receive the first study intervention (Vaccination 1) to which they were randomized and Vaccination 2 to which they were assigned; • Have blood drawn for assay testing within the specified time frame (26-50 days) after Vaccination 2; • Have at least 1 valid and determinate assay result at 4 weeks (26-50 days) after Vaccination 2; • Have no major protocol violations after Vaccination 2.
Vaccination 1 mITT	All randomized participants who receive the study intervention (Vaccination 1) and have at least 1 valid and determinate assay result after Vaccination 1 but before Vaccination 2. The immunogenicity results based on the Vaccination 1 mITT population will be summarized for immunogenicity endpoints if there is a ≥10% difference between the Vaccination 1 mITT population and the Vaccination 1 evaluable immunogenicity population.
Vaccination 2 mITT	All randomized participants who receive the study intervention (Vaccinations 1 and 2) and have at least 1 valid and determinate assay result after Vaccination 2. The immunogenicity results based on the Vaccination 2 mITT population will be summarized for immunogenicity endpoints if there is a ≥10% difference between the Vaccination 2 mITT population and the Vaccination 2 evaluable immunogenicity population.
Vaccination 1 safety	All participants who receive Vaccination 1.
Vaccination 2 safety	All participants who receive Vaccination 2.
Safety	All participants who receive the study intervention.

The major protocol violations will be determined by the medical monitor. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's 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 as appropriate. 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 Vaccinations 1 and 2 evaluable immunogenicity populations.

An additional analysis may be performed based on the mITT populations 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.

All safety and immunogenicity analyses will be performed separately for participants enrolled to receive Vaccinations 1 and 2.

For participants enrolled to receive Vaccination 1, analyses/summary statistics will be presented with vaccine groups (mIRV at various dose levels, bIRV with various dose-level combinations, and qIRV) and corresponding comparator QIV.

For participants consented to get Vaccination 2, analysis/summary statistics will be presented by QIV and mIRV.

For Vaccination 1, analyses/summary will be provided separately for participants receiving QIV within the mIRV, bIRV, or qIRV vaccine groups and for all participants receiving QIV.

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).[3,1]

The CI calculation is described by Collett (1991).[4]

5.2.1.1. Safety Data

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 hematology and chemistry laboratory values, and new ECG abnormalities.

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. The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[5]

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 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 Student's t-distribution, and then exponentiating the confidence limits.

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 (formulation/dose level or control).

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.

The GMR will be calculated within the same vaccine group, or it will be calculated between different vaccine groups. For example, the GMR of HAI titers for each strain in Vaccination 1 recipients compared to Vaccination 2 recipients 4 weeks after each vaccination is an example of calculation within a vaccine group. An example of calculation between vaccine groups is the GMR of HAI titers for each strain in qIRV recipients compared to comparator recipients 4 weeks after Vaccination 1.

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.

5.2.2.5. Cell-Mediated/Humoral Immune Response

The cell-mediated immune response and additional humoral immune response parameters will be summarized for all participants who received Vaccination 1, and all participants or the subset of participants who received Vaccination 1 with PBMC samples collected.

The geometric mean of HA-specific CD4 and CD8 T cells at each time point in which PBMCs were collected and the GMFR for HA-specific CD4 and CD8 T-cell frequencies from before vaccination to each subsequent PBMC collection time point after vaccination will also be provided.

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 Vaccinations 1 and 2 (Section 3.1.1.1).
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety or Vaccination 2 safety population (Section 4).
- Analysis time point: Day 1 through Day 7 after Vaccinations 1 and 2. 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 numerator (n) and denominator (N) used for the calculation of proportion, proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented by vaccine group as specified in Section 5.2, 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, median, minimum, and maximum will be presented by vaccine group as specified in Section 5.2, 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 as specified in Section 5.2 with pooled QIV vaccine groups. 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 Vaccinations 1 and 2 (Section 3.1.1.2).
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety or Vaccination 2 safety population (Section 4).
- Analysis time point: Day 1 through Day 7 after Vaccinations 1 and 2. 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 as specified in Section 5.2. 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 as specified in Section 5.2 with pooled QIV vaccine groups. 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 vaccination through 4 weeks after Vaccinations 1 and 2.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety or Vaccination 2 safety population (Section 4).
- Analysis time point: Day 1 through 4 weeks after Vaccinations 1 and 2.
- 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 through 4 weeks after each 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 as specified in Section 5.2. The AEs will be summarized for each vaccination. That is, for participants who received 2 vaccinations, the AEs will be summarized as follows: 1) AEs from Vaccination 1 to 4 weeks after Vaccination 1; 2) AEs from Vaccination 2 to 4 weeks after Vaccination 2; and 3) all AEs from Vaccination 1 to 4 weeks after Vaccination 2. For participants who received 1 vaccination, the AEs will be summarized from Vaccination 1 to 4 weeks after Vaccination 1.

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The percentage of participants reporting SAEs from vaccination through 6 months after the last vaccination.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety or Vaccination 2 safety population (Section 4).

- Analysis time point: Day 1 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 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 as specified in Section 5.2. The SAEs will be summarized for each vaccination. That is, for participants who received 2 vaccinations, the SAEs will be summarized as follows: 1) SAEs from Vaccination 1 to before Vaccination 2; 2) SAEs from Vaccination 2 to 6 months after Vaccination 2; and 3) all SAEs from Vaccination 1 to 6 months after Vaccination 2. For participants who received 1 vaccination, the SAEs will be summarized from Vaccination 1 to 6 months after Vaccination 1.

6.1.1.5. Hematology and Chemistry Laboratory Parameters

6.1.1.5.1. Abnormal Hematology and Chemistry Laboratory Values

6.1.1.5.1.1. Main Analysis

- Estimand: The percentage of participants with abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety population (Section 4).
- Analysis time points: 2 Days and 1 week after Vaccination 1.
- 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 hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1 (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented for each test within hematology and chemistry by vaccine group as specified in Section 5.2.

6.1.1.5.2. Grading Shifts in Hematology and Chemistry Laboratory Assessments

6.1.1.5.2.1. Main Analysis

- Estimand: The percentage of participants with grading shifts in hematology and chemistry laboratory assessments from baseline to 2 days and 1 week after Vaccination 1.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety population (Section 4).
- Analysis time points: Day 1 (baseline) and 2 days and 1 week after Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing grades will be handled according to Pfizer safety rules.
- Reporting results: The number of participants with grading shifts from baseline to 2 days and 1 week after Vaccination 1 (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented for each test within hematology and chemistry by vaccine group as specified in Section 5.2.

6.1.1.6. Electrocardiograms

6.1.1.6.1. Main Analysis

- Estimand: The percentage of participants with new ECG abnormalities 2 days and 1 week after Vaccination 1.
- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Vaccination 1 safety population (Section 4).
- Analysis time points: 2 Days and 1 week after Vaccination 1.
- 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 and 1 week after Vaccination 1 (n), proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented by vaccine group as specified in Section 5.2.

6.2. Secondary Endpoints

6.2.1. HAI Titers for Each Strain Targeted by Vaccination 1

6.2.1.1. HAI GMTs at 1, 4, and 8 Weeks After Receipt of Vaccination 1

6.2.1.1.1. Main Analysis

- Estimand: HAI GMTs at 1, 4, and 8 weeks after receipt of Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study 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 as specified in Section 5.2 at 1, 4, and 8 weeks after receipt of Vaccination 1.

Figures:

- Empirical RCDCs (Section 5.2.2.4) will be provided for HAI GMTs by vaccine group as specified in Section 5.2 with pooled QIV vaccine groups at Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after Vaccination 1.
- HAI GMTs and associated 95% CIs will be plotted by vaccine group as specified in Section 5.2 with pooled QIV vaccine groups at Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after Vaccination 1.

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 1, 4, and 8 weeks after receipt of Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).

- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study 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 1, 4, and 8 weeks after receipt of Vaccination 1 and associated 2-sided 95% CIs will be provided by vaccine group as specified in Section 5.2.

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 at 1, 4, and 8 weeks after receipt of Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study 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 as specified in Section 5.2 at 1, 4, and 8 weeks after receipt of Vaccination 1.

Figures:

Bar charts with the numbers, proportions, and associated 95% CIs of participants achieving HAI seroconversion for each strain prior to Vaccination 1 and at 1, 4, and 8 weeks after receipt of Vaccination 1, and associated 2-sided Clopper-Pearson 95% CIs, will be plotted by vaccine group as specified in Section 5.2.

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 and 1, 4, and 8 weeks after Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 before Vaccination 1 and 1, 4, and 8 weeks after Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study 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 and 1, 4, and 8 weeks after Vaccination 1 and associated 2-sided Clopper-Pearson 95% CIs will be provided by vaccine group as specified in Section 5.2.

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

6.2.1.1.5.1. Main Analysis

- Estimand: The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study 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) at 1, 4, and 8 weeks after receipt of Vaccination 1 and associated 2-sided Clopper-Pearson 95% CIs will be presented for participants who received 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 1 and at 1, 4, and 8 weeks after receipt of Vaccination 1, and associated 2-sided Clopper-Pearson 95% CIs, will be plotted by vaccine group as specified in Section 5.2.

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

6.2.1.1.6.1. Main Analysis

- Estimand: The proportion of participants with HAI titers ≥1:40 for all strains before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 prior to Vaccination 1 and 1, 4, and 8 weeks after receipt of Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study 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 (targeted by the study vaccine) before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1 and associated 2-sided Clopper-Pearson 95% CIs will be provided for participants who received qIRV or licensed QIV, by vaccine group.

6.2.1.1.7. GMR of HAI Titers for Each Strain in qIRV Recipients Compared to QIV Comparator Recipients 4 Weeks After Vaccination 1

6.2.1.1.7.1. Main Analysis

- Estimand: GMR of HAI titers for each strain in qIRV recipients compared to comparator recipients 4 weeks after Vaccination 1.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).

- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time point: 4 Weeks after Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: GMRs of HAI titers for each strain in qIRV recipients compared to QIV comparator recipients 4 weeks after Vaccination 1 and associated 2-sided 95% CIs will be provided by vaccine group.

6.2.1.1.8. The Difference in Percentages of Participants Achieving Seroconversion for Each Strain at 4 Weeks After Vaccination 1 in qIRV Recipients Compared to QIV Comparator Recipients

6.2.1.1.8.1. Main Analysis

- Estimand: The difference in percentages of participants achieving seroconversion for each strain at 4 weeks after Vaccination 1 in qIRV recipients compared to comparator recipients.
- Estimand strategy: Hypothetical strategies (Section 2.2.2).
- Analysis set: Vaccination 1 evaluable population (Section 4).
- Analysis time points: Day 1 prior to Vaccination 1 and 4 weeks after Vaccination 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing immunogenicity results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: The difference in percentage of participants achieving seroconversion for each strain at 4 weeks after Vaccination 1 in qIRV recipients compared to QIV comparator recipients, and associated 2-sided 95% CIs, will be provided by vaccine group. The 2-sided 95% CIs for the difference in percentages of participants achieving seroconversion between vaccine groups will be calculated using the Miettinen and Nurminen method.

6.3. Tertiary/Exploratory Endpoints

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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, sex, race, and ethnicity) will be generated by vaccine group for Vaccination 1 as specified in Section 5.2 based on the Vaccination 1 safety population.

The number and proportion of participants with at least 1 medical history PT, arranged by SOC, will be tabulated by vaccine group for Vaccination 1 as specified in Section 5.2. The medical history summary is based on the Vaccination 1 safety population.

Participant data listings for demography and baseline characteristics data for Vaccination 1 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 for Vaccination 1 as specified in Section 5.2 based on the Vaccination 1 safety population.

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 as complete if all expected data (the 3 local reactions, the 7 systemic events, fever, and the use of antipyretics) 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 on the 1-day e-diary card. 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:

1. Presence or absence of each local reaction on each day (Day 1-7) after vaccination. 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 days will be summarized by vaccine group for Vaccination 1 as specified in Section 5.2.

The analyses for Vaccination 2 will be applied similarly by vaccine group for Vaccination 2.

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 for Vaccination 1 as specified in Section 5.2. 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.

Participants excluded from the Vaccination 1 evaluable immunogenicity and mITT populations 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 for Vaccination 1 as specified in Section 5.2.

Participant data listings of participants who withdrew during the study will be generated. Also, data listings for participants excluded from the Vaccination 1 evaluable immunogenicity and mITT populations will be generated.

The protocol deviation listings from Vaccination 1 and before Vaccination 2 will be generated. In addition, participants who did not receive Vaccination 1 as assigned will be listed.

The analyses for Vaccination 2 will be applied similarly by vaccine group.

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants randomized and receiving 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 for Vaccination 1 as specified in Section 5.2. The denominator for the percentages is the number of participants randomized in vaccine groups for Vaccination 1 as defined in Section 5.2.

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

A listing of participants showing the randomized vaccine and the vaccine actually received will be presented separately for each vaccine group as described in Section 2.2.1.

The analyses for Vaccination 2 will be applied similarly by vaccine group for all assigned participants.

6.5.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine will be summarized according to the ATC 4th-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 and before Vaccination 2 will be tabulated by vaccine group for Vaccination 1 as specified in Section 5.2. The safety population will be used. Concomitant medications will be summarized in a similar way as concomitant vaccines.

The analyses following Vaccination 2 will be applied similarly by vaccine group. The prior vaccination information will be collected only for Vaccination 1.

6.6. Safety Summaries and Analyses

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

6.6.1. Vital Signs

A descriptive summary, including weight, height, body temperature, pulse rate, and seated blood pressure, based on the Vaccination 1 safety population will be provided in accordance with the Pfizer reporting standards, and listings may be generated.

For Vaccination 2, the summary will be provided for body temperature.

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 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 data accumulated at least 1 week following vaccination with mIRV, bIRV, and qIRV.

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.

4. Collett D. Modelling binary data. 1st ed. London: Chapman & Hall; 1991.

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic therapeutic chemical
bIRV	bivalent influenza modRNA vaccine
BLQ	below the level of quantitation
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
ICD	informed consent document
ICH	International Council for Harmonisation
IFN-γ	interferon gamma
IL-2	interleukin 2
IND	indeterminate
IRC	internal review committee
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
LOD	limit of detection

Abbreviation	Term
MCAR	missing completely at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
MN	microneutralization
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N/A	not applicable
PBMC	peripheral blood mononuclear cell
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient
RBC	red blood cell
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
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
WBC	white blood cell