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

| | |
|---|---|
| **Study Intervention Number:** | PF-07252220 |
| **Study Intervention Name:** | Influenza modRNA vaccine |
| **US IND Number:** | 27600 |
| **EudraCT Number:** | N/A |
| **Protocol Number:** | C4781001 |
| **Phase:** | 1/2 |

**Brief Title:** A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Modified RNA Vaccine Against Influenza

## Document History

| Document | Version Date |
|---|---|
| Amendment 5 | 03 July 2022 |
| Amendment 4 | 08 February 2022 |
| Amendment 3 | 13 January 2022 |
| Amendment 2 | 04 December 2021 |
| Amendment 1 | 14 August 2021 |
| Original protocol | 27 May 2021 |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

## Protocol Amendment Summary of Changes Table

### Amendment 5 (03 July 2022)

### Overall Rationale for the Amendment:

Two hundred and forty participants 18 to 64 years of age were added to Substudy B and will be randomized 1:1 to receive either 1 dose of [redacted] qIRV (encoding 2 A strains and 2 B strains at a dose level of [redacted] or 1 dose of [redacted] qIRV (encoding 2 A strains and 2 B strains at a dose level of [redacted]).

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1 Protocol Summary | Updated to reflect those changes made in the body of the protocol below. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 2.1 Study Rationale | Removed reference to age range of participants solely being 65 to 85 years of age, and added study intervention details of participants 18 to 64 years of age. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 4.1 Overall Design | Removed reference to age range of participants solely being 65 to 85 years of age. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 4.3 Justification for Dose | Updated to reflect administration of 1 dose of [redacted] qIRV in Substudy B. | Addition of participants 18 to 64 years of age in Substudy B, who will receive this study intervention schedule. |
| Section 6.8.1 Prohibited During the Study | Changed timeframe for when receipt of nonstudy influenza vaccine is prohibited to allow for receipt after Visit 207 (8-week follow-up visit). | No blood draw to be taken at Visit 208, and implementation of the study is close to the 2022/2023 influenza season. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.2.5 Pregnancy Testing | Added pregnancy testing requirement for WOCBP. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 9.3.1.2.4 Reverse Cumulative Distribution Curves | Updated language to be consistent with other influenza studies. | Revision to add a bit more details about drawing RCDCs. |
| Section 9.5 Sample Size Determination | Updated sample size information to reflect the addition of 240 participants 18 to 64 years of age in Substudy B. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.4.2 Female Participant Reproductive Inclusion Criteria | Added these standard criteria for participants 18 to 64 years of age. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.10.1 SoA – Substudy B (Phase 1/2) | Added urine pregnancy test for WOCBP. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.10.2.1 Substudy Rationale | Added study intervention details of participants 18 to 64 years of age. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.10.3 Objectives, Endpoints, and Estimands (Substudy B) | Updated primary safety and secondary/exploratory immunogenicity objectives to reflect the addition of participants 18 to 64 years of age in Substudy B.<br><br>Removed estimands relating to seroconversion and HAI ≥1:40 for all heterologous strains. | Addition of participants 18 to 64 years of age in Substudy B.<br><br>Heterologous strains may not all be seasonally related. |
| Section 10.10.4.1 Overall Design | Added details relating to the inclusion of participants 18 to 64 years of age in Substudy B, and updated to reflect prior protocol administrative change letter. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.10.5.1 Substudy B Inclusion Criteria | Updated inclusion criterion 1 and removed inclusion criterion 4 to reflect the addition of participants 18 to 64 years of age in Substudy B. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.10.5.2 Substudy B Exclusion Criteria | Added exclusion criterion 12. | Substudy B enrollment may continue into the 2022 northern hemisphere influenza season. |
| Section 10.10.6.1.1 Administration | Added study intervention details for participants 18 to 64 years of age in Substudy B, and updated to reflect prior protocol administrative change letter. | Addition of participants 18 to 64 years of age in Substudy B. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.10.8.6 Stopping Rules | Updated stopping rules, such that each study intervention dose level will be judged independently and study pauses were applied to the impacted (and higher, if applicable) dose level. | To allow for independent pausing of groups by dose level. |
| Section 10.10.8.8.1 Screening (0 to 28 Days Before Visit 201)<br><br>Section 10.10.8.8.2 Visit 201 – Vaccination 1 (Day 1) | Added urine pregnancy test for WOCBP. | Addition of participants 18 to 64 years of age in Substudy B. |
| Section 10.10.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis<br><br>Section 10.10.9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis<br><br>Section 10.10.9.3.4 Tertiary/Exploratory Endpoint(s) | Updated primary safety and secondary/exploratory immunogenicity estimands to reflect addition of participants 18 to 64 years of age in Substudy B.<br><br>Removed estimands relating to seroconversion and HAI ≥1:40 for all heterologous strains. | Addition of participants 18 to 64 years of age in Substudy B.<br><br>Heterologous strains may not all be seasonally related. |

## TABLE OF CONTENTS

## LIST OF TABLES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Brief Title:**

A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Modified RNA Vaccine Against Influenza.

**Rationale**

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics. Due to the ongoing variability in circulating influenza viruses, recommendations for the viruses to be targeted by each influenza season's vaccines reflect the global influenza virus surveillance that continues throughout the year in both hemispheres. This means that the schedule for vaccine production, release, and administration is highly compressed.

In recent years, the use of mRNA as the basis for potential vaccine candidates has shown increasing promise. Various approaches to optimize the response to mRNA vaccines have been used. This includes modRNA in which some nucleosides are replaced by naturally occurring modified nucleosides, such as pseudouridine, which decreases innate immune activation and increases translation. Two lipid nanoparticle-encapsulated modRNA vaccines encoding the SARS-CoV-2 spike protein have been developed in response to the public health emergency presented by the COVID-19 pandemic: BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), with both vaccines demonstrating high effectiveness with no significant safety concerns during Phase 3 development. Since its first marketing authorization in December 2020, BNT162b2 has been administered to hundreds of millions of individuals worldwide.

Postauthorization safety surveillance in the US has confirmed the safety profile seen in clinical trials, and has also identified adverse reactions of anaphylaxis and an increased risk of myocarditis and pericarditis.

The experience with modRNA-based COVID-19 vaccines supports use of the modRNA platform for potential rapid development of vaccines encoding the seasonally adapted H1, H3, and 2 B HAs for the prevention of influenza. Potential advantages of this platform include accelerated manufacturing, thereby allowing a later decision as to the HA strains to include in the seasonal vaccine, and potentially higher efficacy relative to currently licensed influenza vaccines.

This is a Phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals. This study will be conducted across 2 substudies – Substudy A and Substudy B. Substudy A will describe the safety and immunogenicity of mIRV A or B at 4 dose levels, bIRV encoding both A and B strains in 4 dose-level combinations shown in Section 1.2.1, and qIRV encoding 2 A strains and 2 B strains at a dose level of CCI [redacted].

Additionally, Substudy A will describe:

- The immune response elicited by licensed QIV following prior receipt of a modRNA vaccine, to assess potential priming of the immune response, and
- The immune response elicited by mIRV A or B following prior receipt of licensed QIV, to assess if the immune response following QIV may be enhanced.

Substudy B will describe the safety and immunogenicity of the following vaccination schedules:

In participants 65 to 85 years of age:

- 2 Doses of qIRV encoding 2 A strains and 2 B strains at a dose level of CCI [redacted], 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 [redacted], administered 21 days apart.
- A dose of licensed QIV administered concurrently in the opposite arm with bIRV encoding 2 A strains at a dose level of either CCI [redacted].
- A dose of bIRV encoding 2 A strains at a dose level of CCI [redacted] administered concurrently in the opposite arm with bIRV encoding 2 B strains at a dose level of CCI [redacted].
- A dose of qIRV encoding 2 A strains and 2 B strains at the following dose level combinations:
  - CCI [redacted]
  - [redacted]
  - [redacted]
- A dose of licensed QIV (as a control group).

In participants 18 to 64 years of age:

- 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].

## Objectives, Endpoints, and Estimands

For the purposes of the following 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.

## Substudy A (Phase 1)

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary Safety:** | **Primary Safety:** | **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:<br>• Local reactions for up to 7 days following Vaccinations 1 and 2<br>• Systemic events for up to 7 days following Vaccinations 1 and 2<br>• AEs 4 weeks after Vaccinations 1 and 2<br>• SAEs from the first vaccination to 6 months after the last vaccination<br><br>The percentage of participants with:<br>• Abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1<br>• Grading shifts in hematology and chemistry laboratory assessments between baseline and 2 days and 1 week after Vaccination 1<br><br>The percentage of participants with:<br>• New ECG abnormalities 2 days and 1 week after Vaccination 1 | • Local reactions (pain at the injection site, redness, and swelling)<br>• Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)<br>• AEs<br>• SAEs<br><br>Hematology and chemistry laboratory parameters detailed in Section 10.2<br><br>ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 8.2.7 |

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Secondary:** | **Secondary:** | **Secondary:** |
| 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:<br>• HAI GMTs at 1, 4, and 8 weeks after receipt of Vaccination 1<br>• HAI GMFR from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1<br>• The proportion of participants achieving HAI seroconversion for each strain at 1, 4, and 8 weeks after receipt of Vaccination 1<br>• 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 | HAI titers for each strain targeted by the study vaccine |
| | 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:<br>• The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of Vaccination 1<br>• 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<br>• GMR of HAI titers for each strain in qIRV recipients compared to comparator recipients 4 weeks after Vaccination 1<br>• 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 |
| **Tertiary/Exploratory:** | **Tertiary/Exploratory:** | **Tertiary/Exploratory:** |
| CCI [redacted] | [redacted] | [redacted] |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | CCI [redacted] | |
| [redacted] | [redacted] | [redacted] |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | [redacted] CCI [redacted] | |
| | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

## Substudy B (Phase 1/2)

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary Safety:** | **Primary Safety:** | **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:<br>• Local reactions for up to 7 days following each vaccination<br>• Systemic events for up to 7 days following each vaccination<br>• AEs from the first vaccination to 4 weeks after the last vaccination<br>• SAEs from the first vaccination to 6 months after the last vaccination | • Local reactions (pain at the injection site, redness, and swelling)<br>• Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)<br>• AEs<br>• SAEs |
| | The percentage of participants with:<br>• Abnormal troponin I laboratory values 2 days after the last vaccination | Troponin I laboratory parameters detailed in Section 10.2 |
| | The percentage of participants with:<br>• New ECG abnormalities 2 days after the last vaccination | ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 8.2.7 |
| **Secondary:** | **Secondary:** | **Secondary:** |
| 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:<br>• 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<br>• 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<br>• 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<br>• 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 |
| | In participants having 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: | HAI titers for each strain targeted by the study vaccine |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | • 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<br>• 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 | |
| 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:<br>• HAI GMTs before vaccination and at 1, 4, and 8 weeks after receipt of vaccination<br>• HAI GMFR from before vaccination to 1, 4, and 8 weeks after receipt of vaccination<br>• The proportion of participants achieving HAI seroconversion for each strain at 1, 4, and 8 weeks after receipt of vaccination<br>• 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<br>• The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of vaccination<br>• 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 |
| **Tertiary/Exploratory:** | **Tertiary/Exploratory:** | **Tertiary/Exploratory:** |
| CCI [redacted] | [redacted] | [redacted] |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | CCI | |
| | | |
| | | |

**Overall Design**

This is a Phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals. This study will be conducted across 2 substudies – Substudy A and Substudy B.

**Substudy A (Phase 1)**

This is a Phase 1 randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of qIRV in healthy individuals 65 to 85 years of age.

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

- mIRV at a dose level of CCI encoding A strain, or QIV,
- mIRV at a dose level of CCI, encoding B strain, or QIV,
- bIRV in the dose level combinations shown in the table in Section 1.2, encoding both A and B strains, or QIV, or
- qIRV encoding 2 A strains and 2 B strains at a dose level of CCI, or QIV.

During initial enrollment, each group (vaccine formulation/dose level, or control) will comprise 15 participants 65 to 85 years of age.

Safety data accumulated at least 1 week following Vaccination 1 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 into 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.

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

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

It is anticipated that the following strains will be used in each IRV, but the final strain selection will be detailed in the IP manual:

- mIRV: CCI [redacted]
- bIRV: CCI [redacted] in dose level combinations shown in Section 1.2
- qIRV: CCI [redacted]

**Substudy B (Phase 1/2)**

This is a randomized, single-blinded (sponsor-unblinded) substudy to evaluate the safety and immunogenicity of the vaccination schedules detailed below. The design of Substudy B is summarized in Section 1.2.2.

Participants 65 to 85 years of age will be randomized to one of the following vaccination schedules, 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 [redacted], administered 21 days apart.
- 2 Doses of licensed QIV, administered 21 days apart (as a control group).
- A dose of licensed QIV followed by a dose of bIRV encoding 2 A strains at a dose level of either CCI [redacted], 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 [redacted].
- A dose of bIRV encoding 2 A strains at a dose level of CCI [redacted] administered concurrently in the opposite arm with bIRV encoding 2 B strains at a dose level of CCI [redacted].
- A dose of qIRV encoding 2 A strains and 2 B strains at the following dose level combinations:

  [redacted] CCI [redacted]

- CCI [redacted]
- [redacted]
- A dose of licensed QIV (as a control group).

Substudy B enrollment of participants 65 to 85 years of age will be separated into an initial and expanded enrollment. Depending on the availability of study intervention and operational prioritization, groups of participants 65 to 85 years of age in Substudy B may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time. Participants 18 to 64 years of age will only be included in the study during expanded enrollment – 240 participants 18 to 64 years of age will be randomized 1:1 to receive either a single dose of CCI qIRV (encoding 2 A strains and 2 B strains at a dose level of CCI ) or a single dose of CCI qIRV (encoding 2 A strains and 2 B strains at a dose level of CCI ).

It is anticipated that the following strains will be used in the bIRV, but the final strain selection will be detailed in the IP manual: CCI [redacted]. It is anticipated that the following strains will be used in the qIRV, but the final strain selection will be detailed in the IP manual: CCI [redacted] The strains used in qIRV may vary depending on the time of enrollment relative to the annual influenza season.

**Number of Participants**

Up to approximately 255 participants will be enrolled in Substudy A. Up to approximately 1725 participants will be enrolled in Substudy B (165 participants during initial enrollment, and up to a maximum of 13 groups of 120 participants each being included in the expanded-enrollment stage). The duration of participation for each participant enrolled in either substudy will be up to approximately 8 months.

**Data Monitoring Committee or Other Independent Oversight Committee**

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.

**Statistical Methods**

The following summarizes the statistical methods for both Substudies A and B.

Since the study is descriptive in nature, the planned sample size for the study was not based on any statistical hypothesis testing.

The primary safety objective for the study will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs/SAEs for each vaccine group.

The secondary immunogenicity objectives will be evaluated descriptively by GMT, GMFR, proportion of participants achieving seroconversion measured by HAI, proportion of participants with HAI titers ≥1:40, and the associated 95% CIs, for each strain at the various time points, by vaccine group. Additionally, the GMR of HAI antibody titers from selected modRNA vaccine recipients compared to the comparator group (eg, licensed QIV recipients), and the percentage difference in the proportion of participants achieving seroconversion for each strain at 4 weeks after vaccination, will be described by vaccine group.

## 1.2. Schema

### 1.2.1. Substudy A (Phase 1) Schema

| Vaccination 1 (Initial Enrollment) | | | |
|---|---|---|---|
| IRV Groups | | | Comparator |
| Intervention | Strain(s) | Dose Level(s) | |
| mIRV | A | CCI<br>(N=15/dose level) | Licensed QIV<br>(N=15) |
| mIRV | B | CCI<br>(N=15/dose level) | Licensed QIV<br>(N=15) |
| bIRV | A and B | Dose combinations as shown in table below[a]<br>(N=15/dose combination) | Licensed QIV<br>(N=15) |
| qIRV | 2 x A<br>2 x B | CCI encoding HA of each strain<br>(N=15) | Licensed QIV<br>(N=15) |

| Vaccination 2 (Initial Enrollment) | |
|---|---|
| Licensed QIV<br>(N~195) | mIRV A (CCI; N~30) or<br>mIRV B (CCI; N~30) |

a. **Initial Strain and Dose Level Combinations to Be Used in the bIRV During Substudy A**

| | | B | |
|---|---|---|---|
| | | CCI | CCI |
| A | CCI | | X |
| | CCI | X | X |
| | CCI | | X |

### 1.2.2. Substudy B (Phase 1/2) Schema

| Initial Enrollment (Participants 65 to 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 18 to 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 65 to 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 expanded enrollment who will receive a dose of licensed QIV followed by placebo, administered 21 days apart.

### 1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to Section 10.9.8 for detailed information on each procedure and assessment required for compliance with the protocol regarding Substudy A, and to Section 10.10.8 for Substudy B.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

See Section 10.9.1 for the Substudy A SoA.

See Section 10.10.1 for the Substudy B SoA.

## 2. INTRODUCTION

### 2.1. Study Rationale

This is a Phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals. This study will be conducted across 2 substudies – Substudy A and Substudy B. Substudy A will describe the safety and immunogenicity of mIRV A or B at 4 dose levels, bIRV encoding both A and B strains in the dose-level combinations shown in Table 5, and qIRV encoding 2 A strains and 2 B strains at a dose level of CCI [redacted]. Additionally, Substudy A will describe:

- The immune response elicited by licensed QIV following prior receipt of a modRNA vaccine, to assess potential priming of the immune response, and
- The immune response elicited by mIRV A or B following prior receipt of licensed QIV, to assess if the immune response following QIV may be enhanced.

Safety and immunogenicity data reported to date from Substudy A are detailed in the IB. In summary, following review of the safety data from Substudy A up to 1 week following Vaccination 1 in all groups, no safety concerns have been identified. Specifically, 1-week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in Substudy A showed most events to be mild to moderate in severity, with the most common events being pain at the injection site, fatigue, and headache.

Immunogenicity data up to 1 week following Vaccination 1 in Substudy A showed:

- The proportion of participants achieving seroconversion following administration of mIRV encoding A or B strain increased in a dose-dependent manner.
- The proportion of participants achieving seroconversion 1 week following administration of mIRV at a dose level of CCI [redacted] encoding A strain was 71.4% compared to 53.7% of participants having received licensed QIV.

- The proportion of participants achieving seroconversion 1 week following administration of mIRV at a dose level of CCI encoding B strain was 42.9% compared to 23.8% of participants having received licensed QIV.

- Potential interference in the immune response elicited against B strain was observed when mIRVs encoding A and B strains were combined and administered as bIRV, eg, the proportion of participants achieving seroconversion 1 week following administration of bIRV at a dose level of CCI encoding A strain and CCI encoding B strain was 6.7% for B strain compared to 25.0% of participants having received mIRV at a dose level of CCI encoding B strain.

- The difference in the proportion of participants achieving seroconversion against CCI 1 week following Vaccination 1 was 29.8%, 27.4%, -8.2%, and 0.0%, respectively, when comparing participants who received qIRV to those who received licensed QIV.

These data support exploration of alternative vaccination schedules incorporating IRV, which are included in Substudy B.

Substudy B will describe the safety and immunogenicity of the following vaccination schedules:

In participants 65 to 85 years of age:

- 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 followed by a dose of bIRV encoding 2 A strains at a dose level of either CCI, administered 21 days apart.

- 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).

In participants 18 to 64 years of age:

- 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]

## 2.2. Background

### 2.2.1. Influenza

Influenza is a major cause of morbidity and mortality worldwide, occurring in annual seasonal epidemics and occasionally in global pandemics.[1] Symptomatic influenza infection causes a febrile illness with respiratory and systemic symptoms,[2] although it may often be asymptomatic.[3] The risk of complications and hospitalization from influenza are higher in people ≥65 years of age, young children, and people with certain underlying medical conditions. In the US, an average of >200,000 hospitalizations per year are related to influenza,[4] while the annual global number of deaths is estimated to range from almost 300,000 to over 600,000.[5]

Influenza viruses are part of the *Orthomyxoviridae* family and are divided into 3 genera or types (A, B, and C) based upon antigenic differences in the nucleoprotein and the matrix protein. Influenza A viruses are further classified into subtypes based upon the membrane glycoproteins, HA and NA.[6] The RNA genome is segmented, which allows genetic reassortment among viruses of the same type.[6] This genetic instability can result in the phenomenon known as antigenic shift, involving a major change in 1 or both of the HAs and NAs, which, if efficiently transmissible, can result in a pandemic. More common are multiple point mutations in the genome, leading to more minor changes in the HA and NA, known as antigenic drift.[4] This genetic instability is what necessitates vaccines that are tailored annually.[4]

### 2.2.2. Influenza Vaccination

The first influenza vaccines were licensed in the 1940s,[7] and now a number of different types of vaccine exist: inactivated, recombinant, and LAIV.[8] The viruses that form the basis for inactivated vaccines are replicated in either embryonated hens' eggs or mammalian cell lines,[9] and some are combined with an adjuvant, such as MF59, to improve the immune response, particularly important in older individuals.[8] Multivalent vaccines are produced for routine seasonal immunization, targeting 3 or 4 influenza viruses.[8] Trivalent vaccines target 2 A subtypes and 1 B virus, although in recent years these have been replaced by quadrivalent vaccines which target an additional B virus (to cover 2 antigenically distinct lineages).[10] Standard inactivated vaccines generally contain 15 µg of each HA for adult intramuscular injection, although the high-dose inactivated vaccine contains 60 µg of each HA.[11]

Due to the ongoing variability in circulating influenza viruses, recommendations for the viruses to be targeted by each influenza season's vaccines reflect the global influenza virus surveillance that continues throughout the year in both hemispheres.[11] This means that the schedule for vaccine production, release, and administration is highly compressed.

#### 2.2.2.1. Assessing Influenza Vaccine Immunogenicity

Dependent upon the components included in each influenza vaccine, vaccination is intended to induce antibodies against HA and NA.[12] Strain-specific immunogenicity can be measured by the HAI and microneutralization assays, although antibody titers measured by the HAI are most commonly used to assess vaccine responses.[11] In general, an HAI titer between 1:32 and 1:40 is considered protective at a group level.[11] This is reflected in regulatory guidance, where, for example:

**Seroconversion** is defined as a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40 or a prevaccination HAI titer ≥1:10 and a minimum 4-fold rise in postvaccination HAI antibody titer.[11]

**A reasonable statistical correlate for an efficacy of 50%-70% against clinical symptoms of influenza** is defined as an HAI titer of 1:40.[13]

Regulatory guidance allows for authorization of a new seasonal influenza vaccine on the basis of immunogenicity and/or efficacy data.[13,14]

### 2.2.3. Nucleoside-Modified mRNA Vaccines

In recent years, the use of mRNA as the basis for potential vaccine candidates has shown increasing promise.[15] Various approaches to optimize the response to mRNA vaccines have been used. This includes modRNA, in which some nucleosides are replaced by naturally occurring modified nucleosides, such as pseudouridine, that decrease innate immune activation and increase translation.[15]

Two lipid nanoparticle-encapsulated modRNA vaccines encoding the SARS-CoV-2 spike protein have been developed in response to the public health emergency presented by the COVID-19 pandemic: BNT162b2 (Pfizer/BioNTech)[16] and mRNA-1273 (Moderna).[17] ModRNA vaccine candidate dose levels up to 100 µg[18] and 250 µg[17] were studied in the candidate selection/dose-finding stage of development for the 2 vaccines, respectively. Phase 3 development in participants >12 years of age was conducted with 2 doses of BNT162b2 30 µg[16] and 2 doses of mRNA-1273 100 µg,[19] with both vaccines demonstrated to be highly effective with no identified significant safety concerns.[16,19] Since its first marketing authorization in December 2020, BNT162b2 has been administered to hundreds of millions of individuals worldwide.[20,21] Postauthorization safety surveillance in the US has confirmed the safety profile seen in clinical trials, and has also identified adverse reactions of anaphylaxis and an increased risk of myocarditis and pericarditis.[22]

### 2.2.4. Potential for mRNA Influenza Vaccines

The experience with modRNA-based COVID-19 vaccines supports use of the modRNA platform for potential rapid development of vaccines encoding the seasonally adapted H1, H3, and 2 B HAs for the prevention of influenza.

The modRNA platform would present a number of potential advantages. Manufacturing could be accelerated as no reassortant step is required to produce manufacturing strains. This allows the decision on HA sequence to be made later than with current vaccines, and no egg adaptation is required, reducing the probability of vaccine being mismatched with circulating strains. The induction of not only anti-HA antibodies but also potential CD4+ and CD8+ T-cell responses (as seen with BNT162b2)[23] could improve upon the efficacy observed with existing influenza vaccines.

Similar advantages would also be highly relevant to a pandemic influenza vaccine in the event that one is required.

## 2.3. Benefit/Risk Assessment

modRNA vaccines expressing the SARS-CoV-2 spike protein have been shown to be safe, adequately tolerated, and efficacious in the prevention of COVID-19 when administered as 2 doses at a 21- to 28-day interval.[16,19] These vaccines have been authorized in many countries around the world, and following receipt of the first temporary authorization approximately 774,478,440 doses of BNT162b2 have been shipped worldwide (from 01 December 2020 through 18 June 2021).[21]

This supports use of the modRNA platform for potentially rapid development of vaccines encoding the seasonally adapted H1, H3, and 2 B HAs for the prevention of influenza.

### 2.3.1. Risk Assessment

| Identified/Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention: mIRV, bIRV, qIRV** | | |
| Local and systemic reactions to the vaccine may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, chills, muscle pain, and joint pain) following vaccination. | These are common adverse reactions seen with other vaccines,[24] as well as the COVID-19 vaccine BNT162b2, which is also based on modRNA. The most common events reported in a large-scale efficacy study with BNT162b2 (C4591001) were mild to moderate pain at the injection site, fatigue, and headache.[16] 1-Week follow-up reactogenicity data of 194 participants who received mIRV, bIRV, or qIRV in Substudy A showed most events to be mild to moderate in | The study employs the use of a reactogenicity e-diary which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol.<br>All study participants will be observed for at least 30 minutes after vaccination. |

| Identified/Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | severity, with the most common events being pain at the injection site, fatigue, and headache. | |
| The safety profile of a novel vaccine is not yet fully characterized. | Although qIRV/bIRV/mIRV are novel vaccines, they are based on the same platform (modRNA) as the COVID-19 vaccine BNT162b2, which has been shown to have a positive benefit/risk profile. | AE and SAE reports will be collected from the signing of the ICD to 4 weeks and 6 months, respectively, after the vaccination.<br><br>All participants will be observed for at least 30 minutes after vaccination. |
| Administration of bIRV or qIRV at a total dose of CCI . | This is supported by an acceptable tolerability profile for a single dose up to CCI and opportunity to increase the immune response. | Participants receiving CCI will be vaccinated in a stepwise manner, to ensure that initial tolerability is acceptable prior to dosing of the whole group (see Section 10.10.4.1).<br>AE and SAE reports will be collected from the signing of the ICD to 4 weeks and 6 months, respectively, after vaccination.<br><br>All participants will be observed for at least 30 minutes after vaccination. |
| Unknown safety profile of mIRV A/B administered within at least 8 weeks after QIV. | Administration of mIRV A/B following QIV will allow an assessment of whether the immune response elicited by QIV may be augmented by a modRNA influenza vaccine. | AE and SAE reports will be collected from the signing of the ICD to 4 weeks and 6 months, respectively, after the mIRV A/B vaccination.<br><br>All participants will be observed for at least 30 minutes after vaccination. |
| Unknown safety profile of bIRV administered concurrently with QIV. | Concurrent administration of bIRV with licensed QIV will allow an assessment of whether the immune response elicited by QIV may be augmented by a modRNA influenza vaccine. | AE and SAE reports will be collected from the signing of the ICD to 4 weeks and 6 months, respectively, after the bIRV A/A vaccination.<br><br>All participants will be observed for at least 30 minutes after vaccination. |
| Cases of anaphylaxis, myocarditis, and pericarditis have been reported after authorization in recipients of BNT162b2.[21] | Anaphylaxis: The estimated rate is 5.0 per million doses administered.[25]<br><br>Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within several days after vaccination. These are generally mild cases, and individuals tend to recover | Based on the immunogenicity results at the Phase 3 interim analysis, participants who were randomized to receive qIRV may be offered a licensed QIV.<br>Specific reference to these risks is made within the ICD, with instruction to contact a healthcare professional if a case is suspected.<br>For anaphylaxis, there is an on-site 30-minute observation period after vaccination.<br>Routine ECG and biochemistry monitoring in first week after vaccination. Instructions for handling suspected cases of myocarditis and |

| Identified/Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients. | pericarditis are found in Section 10.9.8.8.11. |
| **Study Intervention: QIV** | | |
| Local and systemic reactions to the vaccine may occur. | The QIV to be used in this study is unknown at the time of protocol authorship. However, the most common local reactions and systemic events observed following vaccination with seasonal influenza vaccines are pain at the injection site, injection site erythema and induration, fever, malaise, myalgia, headache, and fatigue.[26] | The study employs the use of a reactogenicity e-diary which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conduct per protocol.<br><br>All study participants will be observed for at least 30 minutes after vaccination. |
| Unknown safety profile of QIV when administered as 2-dose series. | Administration of 2 doses of QIV will act as a control group in Substudy B and allow assessment of whether the immune response elicited by other vaccination groups in Substudy B is superior. | AE and SAE reports will be collected from the signing of the ICD to 4 weeks and 6 months, respectively, after the last vaccination.<br><br>All participants will be observed for at least 30 minutes after vaccination. |
| **Study Procedures** | | |
| Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic. | Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2. | Pfizer will work with sites to ensure appropriate COVID-19 prevention strategies.<br><br>Monitoring for cases of COVID-19 developing during the study, which will be reported as AEs. |
| Venipuncture will be performed during the study. | There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site. | Only appropriately qualified personnel will obtain the blood draw. |

### 2.3.2. Benefit Assessment

Benefits to individual participants are detailed in Section 10.9.2.3 for participants enrolled in Substudy A and in Section 10.10.2.3 for participants enrolled in Substudy B.

### 2.3.3. Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risks to participants participating in the study, the potential risks identified in association with mIRV, bIRV, and qIRV are justified by the anticipated benefits that may be afforded to healthy participants.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of qIRV, mIRV, and bIRV may be found in the IB, which is the SRSD for this study. The SRSD for the comparator agent (QIV) is the US package insert.

## 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

See Section 10.9.3 for the objectives, estimands, and endpoints for Substudy A.

See Section 10.10.3 for the objectives, estimands, and endpoints for Substudy B.

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a Phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of a modRNA vaccine against influenza in healthy individuals. This study will be conducted across 2 substudies – Substudy A and Substudy B.

See Section 10.9.4 for details of the study design for Substudy A.

See Section 10.10.4 for details of the study design for Substudy B.

### 4.2. Scientific Rationale for Study Design

See Section 2.2.4 and Section 2.1.

#### 4.2.1. Diversity of Study Population

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreener for study recruitment purposes will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

#### 4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for the modRNA influenza vaccines used in this study, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. The use of a highly effective method of contraception is required for sexual intercourse involving a WOCBP (see Appendix 4).

### 4.3. Justification for Dose

Based on the extensive experience with the modRNA-based BNT162b2 COVID-19 vaccine at a dose level of CCI Substudy A did not employ dose escalation. All dose levels to be studied for a particular candidate can be enrolled concurrently, up to a dose level of CCI.

Based on preliminary data from Substudy A, Substudy B will study increased doses of influenza modRNA vaccine: either 1 or 2 doses of CCI, 1 dose of CCI, or 1 dose of CCI. This is supported by an acceptable tolerability profile for a single dose up to CCI and opportunity to increase the immune response. Participants in the first group receiving CCI will be vaccinated in a stepwise manner, to ensure that initial tolerability is acceptable prior to dosing of the whole group (see Section 10.10.4.1).

### 4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit.

## 5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 5.1. Inclusion Criteria

See Section 10.9.5.1 for Substudy A inclusion criteria.

See Section 10.10.5.1 for Substudy B inclusion criteria.

### 5.2. Exclusion Criteria

See Section 10.9.5.2 for Substudy A exclusion criteria.

See Section 10.10.5.2 for Substudy B exclusion criteria.

### 5.3. Lifestyle Considerations

#### 5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may

have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

### 5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

### 5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

The following conditions may allow a participant to be randomized once the conditions have resolved and the participant is otherwise eligible. Participants meeting these criteria at Vaccination 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

1. Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration.

2. Receipt of any nonstudy vaccine within 28 days, before study intervention administration.

3. Anticipated receipt of any nonstudy vaccine within 28 days, after study intervention administration.

4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

## 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

### 6.1.1. Administration

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

See Section 10.9.6.1 for study intervention administration details for Substudy A.

See Section 10.10.6.1 for study intervention administration details for Substudy B.

### 6.1.2. Medical Devices

The comparator vaccine detailed in Section 10.9.6.1 and Section 10.10.6.1 may be provided as a PFS and, in which case, should be considered a medical device.

All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

## 6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention once prepared.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

### 6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the preparation and dispensing.

See Section 10.9.6.1.4 for further details regarding study intervention preparation and dispensing for Substudy A.

See Section 10.10.6.1.4 for further details regarding study intervention preparation and dispensing for Substudy B.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

### 6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. This report will be provided to blinded or unblinded site staff as appropriate depending on the role/permission the user is granted and must be stored in the site's blinded or unblinded files as appropriate.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

See Section 10.9.6.2.1 for further details regarding allocation of study intervention in Substudy A.

See Section 10.10.6.2.1 for further details regarding allocation of study intervention in Substudy B.

### 6.3.2. Blinding Arrangements

Substudy A blinding arrangements for site personnel and the sponsor are detailed in Section 10.9.6.2.2 and Section 10.9.6.2.3.

Substudy B blinding arrangements for site personnel and the sponsor are detailed in Section 10.10.6.2.2 and Section 10.10.6.2.3.

## 6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5. Dose Modification

Not applicable.

## 6.6. Continued Access to Study Intervention After the End of the Study

No intervention will be provided to study participants at the end of their study participation.

### 6.7. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

### 6.8. Concomitant Therapy

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

- Prior receipt of any COVID-19 vaccine.
- For Substudy A, licensed influenza vaccine, if received during the prior influenza season.
- For Substudy B, any licensed influenza vaccine received in the prior 12 months.
- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 6 for Substudy A and Visit 207 for Substudy B).
- Prohibited medications listed in Section 6.8.1 will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.
- All current medications at baseline will be recorded and include start date, name of the medication, dose, unit, route, and frequency.

#### 6.8.1. Prohibited During the Study

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 (see Section 7). 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 that contains modRNA for Substudy A, and within 28 days before and 28 days after any study vaccination that contains modRNA for Substudy B.

- For Substudy A, receipt of any other (nonstudy) seasonal influenza vaccine at any time during study participation is prohibited.

- For Substudy B, receipt of any other (nonstudy) seasonal influenza vaccine from enrollment to Visit 207 (8-week follow-up visit) 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.

### 6.8.2. Permitted During the Study

- Medication other than that described as prohibited in Section 6.8.1 required for treatment of preexisting conditions or acute illness is permitted.

- Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: AEs, participant request, investigator request, pregnancy, and protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and immunogenicity. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. Participants who remain in the study for evaluation of safety will be contacted by telephone 6 months after their last study vaccination to record AEs as described in Section 8.3.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

## 7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

### 7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

## 7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

## 8. STUDY ASSESSMENTS AND PROCEDURES

See Section 10.9.8 for assessments and procedures specific to Substudy A, and Section 10.10.8 for assessments and procedures specific to Substudy B.

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Clinical safety laboratory assessments will be collected in this study (see Section 10.2).

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

## 8.1. Efficacy and/or Immunogenicity Assessments

Blood samples will be obtained for immunogenicity testing at the visits specified in the study SoA (see Section 10.9.1 for the Substudy A SoA, and Section 10.10.1 for the Substudy B SoA).

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory.

### 8.1.1. Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed, with the exception of those participants who have provided specific consent to genetic testing of the blood samples for PBMC isolation.

## 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at their first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

Acute reactions within the first 30 minutes after administration of the study intervention will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever) and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.2.3.1.

### 8.2.1. Physical Examinations

A physical examination will be performed at the screening visit and, if clinically indicated, prior to the participant's first vaccination (Visits 1 and 201 for Substudies A and B, respectively). Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to Section 8.3.3.

### 8.2.2. Vital Signs

The participant's body temperature will be measured prior to each vaccination. Additionally, weight, height (at screening), pulse rate, and seated blood pressure will be measured prior to the participants first vaccination.

### 8.2.3. Electronic Diary

Participants will be required to complete a reactogenicity e-diary after each vaccination through an application installed on a provisioned device or on the participant's own personal device. 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 the study intervention. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

#### 8.2.3.1. Grading Scales

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.[24]

#### 8.2.3.2. 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. In Substudy B, 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 vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Participants will be provided with a measuring device. 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 1. 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 1.

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

**Table 1. 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 |

**Table 1. Local Reaction Grading Scale**

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

### 8.2.3.3. 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 2.

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

**Table 2. 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 2. 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.

### 8.2.3.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. 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 and then categorized according to the scale shown in Table 3 during analysis.

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

**Table 3. Scale for Fever**

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

### 8.2.3.5. 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).

### 8.2.4. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be collected in both Substudies A and B. See Section 10.2.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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. Refer to the laboratory normal ranges (provided separately) for grading scales for abnormalities.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Section 10.6 for suggested actions and follow-up assessments in the event of potential DILI.

### 8.2.5. Pregnancy Testing

Following screening, pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant’s receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will not be administered the study intervention dose and will be withdrawn from the study.

### 8.2.6. Stopping Rules

The following stopping rules are in place for both Substudies A and B; see also Section 10.9.8.6 and Section 10.10.8.6, respectively.

### 8.2.7. ECGs and Echocardiograms

ECGs will be collected at the times specified in Section 10.9.1 for Substudy A and Section 10.10.1 for Substudy B.

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, measurement of blood pressure, and measurement of pulse rate. ECGs will be performed in triplicate.

ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 5) and should be evaluated further, as clinically warranted.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that lead placement be in the same position each time in order to achieve precise ECG recordings.

ECG values of potential clinical concern are listed in Appendix 5.

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

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

Echocardiograms may be performed as detailed in Section 10.9.8.8.11 and Section 10.10.8.8.11.

### 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.7. Device deficiencies are covered in Section 8.3.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

### 8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including:

- Visit 4 (4-week follow-up visit), and from Visit 5 to Visit 5B (4-week post–Vaccination 2 follow-up visit) for Substudy A. Additionally, for Substudy A, any AEs occurring up to 48 hours after the blood draws at Visits 4 and 5B must be recorded on the CRF.

- 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.

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

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

#### 8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

#### 8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

### 8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation.

The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

### 8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

#### 8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

#### 8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form must be maintained in the investigator site file.

### 8.3.6. Cardiovascular and Death Events

Not applicable.

### 8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

### 8.3.8. Adverse Events of Special Interest

For all study phases, the following events are considered AESIs:

- A confirmed diagnosis of influenza;

- A confirmed diagnosis of myocarditis or pericarditis. See Section 10.9.8.8.11 and Section 10.10.8.8.11 for additional procedures for monitoring of potential myocarditis or pericarditis in Substudies A and B, respectively.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

#### 8.3.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

### 8.3.9. Medical Device Deficiencies

Medical devices being provided for use in this study as the study intervention may be supplied in PFS. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.7.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Section 8.3.1 through Section 8.3.4 and Appendix 3 of the protocol.

#### 8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the unblinded site staff learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the unblinded site staff will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.7.

#### 8.3.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The unblinded site staff is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the unblinded site staff.

#### 8.3.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The unblinded site staff notifies the sponsor by a contact method as detailed in the IP manual within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or non-serious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.3.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting Form as outlined in Sections 8.3.1.1 and Section 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

#### 8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The unblinded site staff will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The unblinded site staff, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

### 8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

| Safety Event | Recorded on the CRF | Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| Medication errors | All (regardless of whether associated with an AE) | Only if associated with an SAE |

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE**.

### 8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

### 8.5. Genetics

Some of the blood samples collected for PBMC isolation may be used for DNA and/or RNA isolation. The DNA and/or RNA samples from the PBMC isolation may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs, for understanding the B-cell, T-cell, and antibody repertoires.

See Section 10.12 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

### 8.6. Biomarkers

Biomarkers are not evaluated in this study.

### 8.7. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

### 8.8. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

## 9. STATISTICAL CONSIDERATIONS

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

### 9.1. Statistical Hypotheses

Refer to Section 10.9.9 and Section 10.10.9 for Substudy A and Substudy B statistical hypotheses, respectively.

#### 9.1.1. Estimands

Refer to Section 10.9.3 and Section 10.10.3 for estimands relating to Substudy A and Substudy B, respectively.

#### 9.1.2. Multiplicity Adjustment

Please see Section 10.9.9.1.2 and Section 10.10.9.1.2 for Substudy A and Substudy B, respectively.

## 9.2. Analysis Sets

For purposes of analysis for the study, the following analysis sets are defined:

| 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 | For Substudy A only. All participants who are eligible, receive the study intervention (Vaccination 1) to which they were randomized, have blood drawn for assay testing within specified time frames after Vaccination 1, have at least 1 valid and determinate assay result at the 4-week post–Vaccination 1 visit, and have no major protocol violations before Vaccination 2. |
| Vaccination 2 evaluable | All participants who are eligible; receive the first study intervention(s) (Vaccination 1) (1 vaccination, or 2 different vaccinations administrated in the left and right arms) to which they were randomized, and the second study vaccination (Vaccination 2) if they received only 1 vaccination before; have blood drawn for assay testing within specified time frames after Vaccination 2 and have at least 1 valid and determinate assay result at the 4-week post–Vaccination 2 visit, or have blood drawn for assay testing within specified time frames after Vaccination 1 (for participants with 2 vaccinations administrated) and have at least 1 valid and determinate assay result at the 4-week post–Vaccination 1 visit; and have no major protocol violations. |
| Vaccination 1 mITT | For Substudy A only. 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. |
| Vaccination 2 mITT | All randomized participants who receive the study intervention(s) (Vaccination 1 and Vaccination 2; or Vaccination 1 only [2 vaccinations administrated in the left and right arms]) and have at least 1 valid and determinate assay result after Vaccination 2, or have at least 1 valid and determinate assay result after Vaccination 1 (for participants with 2 vaccinations administrated). |
| Safety | All participants who receive the study intervention. |

## 9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the general considerations of statistical analyses.

Refer to appendices for description of the statistical analyses for primary, secondary, and/or exploratory endpoints. Statistical analyses for Substudy A and Substudy B are detailed in Section 10.9.9 and Section 10.10.9, respectively.

### 9.3.1. General Considerations

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 population. 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. Antibody titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

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.

#### 9.3.1.1. Analyses for Binary Data

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

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

#### 9.3.1.2. Analyses for Continuous Data

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

#### 9.3.1.2.1. Geometric Means

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

#### 9.3.1.2.2. Geometric Mean Fold Rises

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

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

#### 9.3.1.2.3. 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.

#### 9.3.1.2.4. 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.

### 9.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

## 9.4. Interim Analyses

Details for interim analyses will be provided in the appendix - Section 10.9.9.4 and Section 10.10.9.4 for Substudy A and Substudy B, respectively.

## 9.5. Sample Size Determination

The study sample size for the study is not based on any statistical hypothesis testing.

Fifteen participants will be enrolled in each group (vaccine formulation/dose level or control) for Vaccination 1 in Substudy A, and also into each group for Vaccination 1 in Substudy B. There are 17 such groups planned to be enrolled in Substudy A; therefore, up to approximately 255 participants in total are planned to be enrolled in Substudy A.

During initial enrollment, there are 11 groups for Vaccination 1 in Substudy B, with approximately 15 participants planned to be enrolled per group. Additionally, following IRC review of safety and immunogenicity at least 1 week following the last vaccination in each group from initial enrollment, a further 120 participants may be enrolled in selected groups, including 2 groups of participants 18 to 64 years of age (expanded enrollment). Therefore, up to approximately 1725 participants are planned to be enrolled in Substudy B.

For safety outcomes in the study, Table 4 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, at various sample sizes.

**Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes**

| | **Assumed True Event Rate of an AE** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sample Size (N)** | **0.01%** | **0.32%** | **0.50%** | **1.0%** | **2.0%** | **5%** | **10%** |
| **15** | 0.00 | 0.05 | 0.07 | 0.14 | 0.26 | 0.54 | 0.79 |
| **30** | 0.00 | 0.09 | 0.14 | 0.26 | 0.45 | 0.79 | 0.96 |
| **45** | 0.00 | 0.13 | 0.2 | 0.36 | 0.6 | 0.9 | 0.99 |
| **60** | 0.01 | 0.17 | 0.26 | 0.45 | 0.7 | 0.95 | >0.99 |
| **90** | 0.01 | 0.25 | 0.36 | 0.6 | 0.84 | 0.99 | >0.99 |
| **120** | 0.01 | 0.32 | 0.45 | 0.7 | 0.91 | >0.99 | >0.99 |
| **135** | 0.01 | 0.35 | 0.49 | 0.74 | 0.93 | >0.99 | >0.99 |
| **150** | 0.01 | 0.38 | 0.53 | 0.78 | 0.95 | >0.99 | >0.99 |
| **195** | 0.02 | 0.46 | 0.62 | 0.86 | 0.98 | >0.99 | >0.99 |
| **270** | 0.03 | 0.58 | 0.74 | 0.93 | >0.99 | >0.99 | >0.99 |
| **275** | 0.03 | 0.59 | 0.75 | 0.94 | >0.99 | >0.99 | >0.99 |
| **410** | 0.04 | 0.73 | 0.87 | 0.98 | >0.99 | >0.99 | >0.99 |
| **420** | 0.04 | 0.74 | 0.88 | 0.99 | >0.99 | >0.99 | >0.99 |
| **445** | 0.04 | 0.76 | 0.89 | 0.99 | >0.99 | >0.99 | >0.99 |
| **540** | 0.05 | 0.82 | 0.93 | >0.99 | >0.99 | >0.99 | >0.99 |
| **695** | 0.07 | 0.89 | 0.97 | >0.99 | >0.99 | >0.99 | >0.99 |
| **815** | 0.08 | 0.93 | 0.98 | >0.99 | >0.99 | >0.99 | >0.99 |
| **945** | 0.09 | 0.95 | 0.99 | >0.99 | >0.99 | >0.99 | >0.99 |
| **1080** | 0.10 | 0.97 | >0.99 | >0.99 | >0.99 | >0.99 | >0.99 |
| **1215** | 0.11 | 0.98 | >0.99 | >0.99 | >0.99 | >0.99 | >0.99 |
| **1350** | 0.13 | 0.99 | >0.99 | >0.99 | >0.99 | >0.99 | >0.99 |
| **1485** | 0.14 | 0.99 | >0.99 | >0.99 | >0.99 | >0.99 | >0.99 |

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

#### 10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

### 10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

### 10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

### 10.1.5. Committees Structure

#### 10.1.5.1. Data Monitoring Committee

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. The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter.

The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators, as appropriate.

The responsibilities of the IRC will include at a minimum:

- Review of safety data in the case of a stopping rule being met.
- For Substudy A, review of safety data accumulated at least 1 week following vaccination with mIRV, bIRV, and qIRV at Visit 1.

- For Substudy B, review of safety and immunogenicity data accumulated at least 1 week following the last vaccination in each group.

### 10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

### 10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory retain notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

### 10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the study monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the study monitoring plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

### 10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

### 10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer

intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

### 10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

## 10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in Section 10.9.1 for Substudy A and Section 10.10.1 for Substudy B. 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.

| **Substudy A** | |
|---|---|
| **Hematology** | **Chemistry** |
| Hemoglobin<br>Hematocrit<br>RBC count<br>MCV<br>MCH<br>MCHC<br>Platelet count<br>WBC count<br>Total neutrophils (Abs)<br>Eosinophils (Abs)<br>Monocytes (Abs)<br>Basophils (Abs)<br>Lymphocytes (Abs) | BUN and creatinine<br>AST, ALT<br>Total bilirubin<br>Alkaline phosphatase<br>Cardiac troponin I<br>C-reactive protein |
| **Substudy B** | |
| **Hematology** | **Chemistry** |
| N/A | Cardiac troponin I |

Please refer to the laboratory normal ranges (provided separately) for grading scales for abnormalities.

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.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Investigators must document their review of each laboratory safety report.

## 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

### 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br>• Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:<br>  • Is associated with accompanying symptoms.<br>  • Requires additional diagnostic testing or medical/surgical intervention.<br>  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.<br>• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.<br><br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.<br><br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br><br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br><br>• Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

### 10.3.2. Definition of an SAE

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br><br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br><br>In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br><br>Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE. |

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.**

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

**g. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

| Safety Event | Recorded on the CRF | Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| SAE | All | All |
| Nonserious AE | All | None |
| Exposure to the study intervention under study during pregnancy or breastfeeding. | All AEs or SAEs associated with exposure during pregnancy or breastfeeding.<br><br>**Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF. | All instances of EDP are reported (whether or not there is an associated SAE).*<br><br>All instances of EDB are reported (whether or not there is an associated SAE). ** |
| Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB). | None. Exposure to a study non-participant is not collected on the CRF. | The exposure (whether or not there is an associated AE or SAE) must be reported.*** |

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

| **Follow-Up of AEs and SAEs** |
|---|
| • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.<br><br>• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.<br><br>• New or updated information will be recorded in the originally submitted documents.<br><br>• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information. |

### 10.3.4. Reporting of SAEs

| **SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form** |
|---|
| • Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.<br><br>• In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.<br><br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames. |

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

### 10.4.2. Female Participant Reproductive Inclusion Criteria

For Substudy A and participants 65 to 85 years of age at the time of enrollment in Substudy B, a female participant is eligible to participate if she is not pregnant or breastfeeding, and is not a WOCBP (see definitions below in Section 10.4.3).

For Substudy B participants 18 to 64 years of age at the time of enrollment, the criteria below are part of inclusion criterion 1 (Age and Sex; Section 10.10.5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).
    - OR

- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

### 10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

- A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

   - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;

   - Intravaginal;

   - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;

   - Injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated

in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

## 10.5. Appendix 5: ECG Findings of Potential Clinical Concern

| ECG Findings That May Qualify as AEs |
|---|
| • Marked sinus bradycardia (rate <40 bpm) lasting minutes.<br>• New PR interval prolongation >280 msec.<br>• New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.<br>• New-onset atrial flutter or fibrillation, with controlled ventricular response rate, ie, rate <120 bpm.<br>• New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.<br>• Frequent PVCs, triplets, or short intervals (<30 sec) of consecutive ventricular complexes. |
| **ECG Findings That May Qualify as SAEs** |
| • QTcF prolongation >500 msec.<br>• New ST-T changes suggestive of myocardial ischemia.<br>• New-onset left bundle branch block (QRS >120 msec).<br>• New-onset right bundle branch block (QRS >120 msec).<br>• Symptomatic bradycardia.<br>• Asystole:<br>  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;<br>  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;<br>  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.<br>• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute). |

- Ventricular rhythms of >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm, such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

**ECG Findings That Qualify as SAEs**

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team and are not to be considered as all inclusive of what is to be reported as an AE or SAE.

## 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

### Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in Substudy B. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities**.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

## 10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

**Definitions of a Medical Device Deficiency**

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

### 10.7.1. Definition of AE and ADE

| AE and ADE Definition |
|---|
| • An AE is defined in Appendix 3 (Section 10.3.1).<br>• An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. |

### 10.7.2. Definition of SAE, SADE, and USADE

| SAE Definition |
|---|
| • An SAE is defined in Appendix 3 (Section 10.3.2). |
| **SADE Definition** |
| • An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.<br>• Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. |

| **USADE Definition** |
| --- |
| • A USADE is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file. |

### 10.7.3. Definition of Device Deficiency

| **Device Deficiency Definition** |
| --- |
| • A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer. |

### 10.7.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

| **Device Deficiency Recording** |
| --- |
| • When a device deficiency occurs, it is the responsibility of the unblinded site staff to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.<br>• The unblinded site staff will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint form.<br>• It is **not** acceptable for the unblinded site staff to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form.<br>• There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.<br>• If the unblinded site staff determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3). |

- For device deficiencies, it is very important that the unblinded site staff describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

**Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency**

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the product information in his/her assessment.
- For each device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

| **Follow-Up of Medical Device Deficiency** |
|---|
| • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.<br>• New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form.<br>• New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3. |

### 10.7.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

### 10.7.6. Reporting of SADEs

| **SADE Reporting to Pfizer Safety** |
|---|
| Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, a SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.<br>• Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.<br>• The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations. |

## 10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

### 10.8.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record details of any of the prohibited medications specified in Section 6.8.1 received by the participant if required for his or her clinical care.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

## 10.9. Appendix 9: Substudy A (Phase 1)

### 10.9.1. SoA – Substudy A (Phase 1)

| Visit Number | Screening | 1 | 2 | 3 | 4 | 5 | 5A | 5B | 6 |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Screening** | **Vaccination** | **Day 3 Follow-up Visit** | **1-Week Follow-up Visit** | **4-Week Follow-up Visit** | **8-Week Follow-up Visit** | **Vaccination 2** | **4-Week Post–Vaccination 2 Follow-up Visit** | **6-Month Telephone Contact** |
| **Visit Window (Days)** | **0 to 28 Days Before Visit 1** | **Day 1** | **2-4 Days After Visit 1** | **6 to 8 Days After Visit 1** | **26 to 30 Days After Visit 1** | **52 to 60 Days After Visit 1** | **52 to 97 Days After Visit 1[a]** | **26 to 45 Days After Vaccination at Visit 5 or 5A[b]** | **175 to 189 Days After Last Study Vaccination** |
| Obtain informed consent | X | | | | | X | X | X | |
| Assign participant number | X | | | | | | | | |
| Obtain demography and medical history data | X | | | | | | | | |
| Obtain details of medications currently taken | X | | | | | | | | |
| Perform physical examination | X | | | | | | | | |
| Perform clinical assessment | | X | | | | | | | |
| Measure vital signs (including body temperature) | X | X | X | | | | | | |
| Measure body temperature | | | | | | X | X | | |
| Collect blood sample for hematology and chemistry laboratory tests | ~20 mL | ~20 mL | ~20 mL | ~20 mL | | | | | |
| Perform 12-lead triplicate ECG | X | X | X | X | | | | | |
| Collect prior COVID-19 vaccine information | X | | | | | | | | |
| Collect prior licensed influenza vaccine information from the last season | X | | | | | | | | |
| Collect nonstudy vaccine information | X | X | X | X | X | X | X | X | X |
| Confirm eligibility | X | X | | | | | X | | |
| Collect prohibited medication use | | | X | X | X | X | X | X | |
| Review hematology, chemistry, and ECG results | | X | X | X | X | | | | |

| Visit Number | Screening | 1 | 2 | 3 | 4 | 5 | 5A | 5B | 6 |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Screening** | **Vaccination** | **Day 3 Follow-up Visit** | **1-Week Follow-up Visit** | **4-Week Follow-up Visit** | **8-Week Follow-up Visit** | **Vaccination 2** | **4-Week Post–Vaccination 2 Follow-up Visit** | **6-Month Telephone Contact** |
| **Visit Window (Days)** | **0 to 28 Days Before Visit 1** | **Day 1** | **2-4 Days After Visit 1** | **6 to 8 Days After Visit 1** | **26 to 30 Days After Visit 1** | **52 to 60 Days After Visit 1** | **52 to 97 Days After Visit 1[a]** | **26 to 45 Days After Vaccination at Visit 5 or 5A[b]** | **175 to 189 Days After Last Study Vaccination** |
| Confirm use of contraceptives (if appropriate) | X | X | X | X | X | X | X | | |
| Obtain randomization number and study intervention allocation | | X | | | | | | | |
| Collect blood sample for immunogenicity assessment | | ~50 mL | | ~50 mL | ~50 mL | ~50 mL | ~50 mL[c] | ~50 mL | |
| Collect blood sample for cell-mediated immunogenicity assessment[d] | | ~50 mL | | ~50 mL | ~50 mL | | | | |
| Administer blinded study intervention | | X | | | | | | | |
| Unblind participant's vaccine assignment | | | | | | X | | | |
| Administer licensed influenza vaccine[e] | | | | | | X | | | |
| Administer open-label mIRV A or B, as appropriate[f] | | | | | | | X | | |
| Assess acute reactions for at least 30 minutes after study intervention administration | | X | | | | X | X | | |
| Explain to the participant e-diary completion requirements and assist the participant with downloading the app or issue provisioned device if required | | X | | | | X | X | | |
| Provide thermometer and measuring device | | X | | | | X | X | | |
| Review reactogenicity e-diary data (daily review is optimal during the active diary period) | | ◄ | ——— | ——— | ► | ◄ | ——— | ► | |

| Visit Number | Screening | 1 | 2 | 3 | 4 | 5 | 5A | 5B | 6 |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Screening** | **Vaccination** | **Day 3 Follow-up Visit** | **1-Week Follow-up Visit** | **4-Week Follow-up Visit** | **8-Week Follow-up Visit** | **Vaccination 2** | **4-Week Post–Vaccination 2 Follow-up Visit** | **6-Month Telephone Contact** |
| **Visit Window (Days)** | **0 to 28 Days Before Visit 1** | **Day 1** | **2-4 Days After Visit 1** | **6 to 8 Days After Visit 1** | **26 to 30 Days After Visit 1** | **52 to 60 Days After Visit 1** | **52 to 97 Days After Visit 1[a]** | **26 to 45 Days After Vaccination at Visit 5 or 5A[b]** | **175 to 189 Days After Last Study Vaccination** |
| Review ongoing reactogenicity e-diary symptoms and obtain stop dates | | | | X | X | | | X | |
| Collect AEs and SAEs as appropriate | X | X | X | X | X[g] | X | X | X | X |
| Collect e-diary or assist the participant with deleting application | | | | X[h] | X | | | X | |

Abbreviations: COVID-19 = coronavirus disease 2019; ECG = electrocardiography; SoA = schedule of activities.

a. Visit 5A procedures for participants who received QIV at Visit 1 only. Visit 5 and 5A procedures may be conducted at the same visit, depending on the timing of these visits relative to implementation of protocol amendment 2.
b. Visit 5B to be conducted 26 to 45 days after either Visit 5 or Visit 5A, depending on at which visit Vaccination 2 was performed.
c. Blood draw at Visit 5A to be conducted prior to vaccination only if Visit 5 and 5A procedures are being conducted as separate visits.
d. Additional 50 mL for cell-mediated immunogenicity assessments as detailed in Section 10.9.4.1.
e. Individual participants will be unblinded and licensed influenza vaccine administered at Visit 5 to participants not having previously received seasonal QIV.
f. Either mIRV A or mIRV B to be administered to participants having received QIV at Visit 1.
g. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3).
h. If Visit 3 is conducted after Day 7.

### 10.9.2. Introduction

#### 10.9.2.1. Substudy Rationale

Substudy A is a Phase 1 randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety and immunogenicity of:

- Various dose levels of mIRV and bIRV encoding A and/or B strain(s) in participants 65 to 85 years of age, and
- qIRV encoding 2 A strains and 2 B strains at a dose level of [redacted]. See Section 10.9.4 for more details regarding the design.

#### 10.9.2.2. Background

See Section 2.2.

#### 10.9.2.3. Benefit/Risk Assessment

In addition to those risks detailed in Section 2.3, the following additional risks are noted for Substudy A:

- Unknown safety profile of mIRV A/B administered approximately 8 weeks after QIV – this risk is justified in order to describe whether the immune response elicited by QIV may be augmented by a modRNA influenza vaccine. However, in order to mitigate this risk, AE and SAE reports will be collected from the signing of the ICD to 4 weeks after the vaccination, and all participants will be observed for at least 30 minutes after mIRV A/B vaccination.

Benefits to individual participants enrolled in Substudy A may be:

- Receipt of a potentially efficacious influenza vaccine at no cost to the participant, and provision of the immunogenicity results following administration.
- Receipt of a licensed seasonal influenza vaccine at no cost to the participant.
- Contributing to research to help others.

Please see Section 2.3.3 for details of the SRSDs relating to study intervention used in Substudy A.

### 10.9.3. Objectives, Endpoints, and Estimands (Substudy A)

For the purposes of the study 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.

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary Safety:** | **Primary Safety:** | **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:<br>• Local reactions for up to 7 days following Vaccinations 1 and 2<br>• Systemic events for up to 7 days following Vaccinations 1 and 2<br>• AEs 4 weeks after Vaccinations 1 and 2<br>• SAEs from the first vaccination to 6 months after the last vaccination | • Local reactions (pain at the injection site, redness, and swelling)<br>• Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)<br>• AEs<br>• SAEs |
| | The percentage of participants with:<br>• Abnormal hematology and chemistry laboratory values 2 days and 1 week after Vaccination 1<br>• Grading shifts in hematology and chemistry laboratory assessments between baseline and 2 days and 1 week after Vaccination 1 | • Hematology and chemistry laboratory parameters detailed in Section 10.2 |
| | The percentage of participants with:<br>• New ECG abnormalities 2 days and 1 week after Vaccination 1 | ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 8.2.7 |
| **Secondary:** | **Secondary:** | **Secondary:** |
| 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:<br>• HAI GMTs at 1, 4, and 8 weeks after receipt of Vaccination 1<br>• HAI GMFR from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1<br>• 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 |

| 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:<br>• The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of Vaccination 1<br>• 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<br>• GMR of HAI titers for each strain in qIRV recipients compared to comparator recipients 4 weeks after Vaccination 1<br>• 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 |
| **Tertiary/Exploratory:** | **Tertiary/Exploratory:** | **Tertiary/Exploratory:** |
| CCI [redacted] | [redacted] | [redacted] |
| | [redacted] | |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | [redacted] CCI [redacted] | |
| [redacted] | [redacted] | [redacted] |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | CCI | |
| | | |

### 10.9.4. Substudy A Design

#### 10.9.4.1. Overall Design

This is a randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety and immunogenicity of mIRV and bIRV encoding both A and B strains in the dose-level combinations shown in Table 5, and qIRV, in participants 65 to 85 years of age.

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

- mIRV at a dose level of CCI encoding A strain, or QIV,
- mIRV at a dose level of CCI, encoding B strain, or QIV,
- bIRV in the dose level combinations shown in Table 5 below, encoding both A and B strains, or QIV, or
- qIRV encoding 2 A strains and 2 B strains at a dose level of CCI, or QIV.

**Table 5. Initial Strain and Dose Level Combinations to Be Used in the bIRV During Substudy A**

| | | B Strain | |
|---|---|---|---|
| | | CCI | CCI |
| 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) will comprise 15 participants.

Safety data accumulated at least 1 week following Vaccination 1 with mIRV, bIRV, and qIRV will be reviewed and, if deemed acceptable, a further 360 participants can be enrolled (expanded enrollment) 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.

All participants will be asked to complete a reactogenicity e-diary for 7 days following Vaccination 1. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to vaccination on Day 1 and at 1, 4, and 8 weeks after Vaccination 1. The total duration of the study for each participant will be up to approximately 8 months.

All participants will be asked to provide an additional blood sample of approximately 20 mL at time points specified in Section 10.9.1 for assessment of hematology and chemistry laboratory tests.

All participants enrolled prior to expanded enrollment will be asked to provide an additional blood sample of 50 mL at time points specified in Section 10.9.1 for assessment of cell-mediated immunogenicity.

It is anticipated that the following strains will be used in each IRV, but the final strain selection will be detailed in the IP manual:

- mIRV: CCI [redacted]
- bIRV: CCI [redacted] in dose level combinations shown in Section 1.2
- qIRV: CCI [redacted]

Dependent upon safety and/or immunogenicity data generated during this phase, it is possible that additional bIRV groups may be initiated to study further dose level and strain combinations.

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 QIV at Visit 1 will receive either:

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

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

Following implementation of protocol amendment 2, all participants will be asked to complete a reactogenicity e-diary for 7 days following Vaccination 2. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to Vaccination 2 and 4 weeks afterwards.

### 10.9.4.2. Scientific Rationale for Study Design

See Section 2.1.

### 10.9.4.3. Justification for Dose

See Section 4.3.

### 10.9.4.4. End of Study Definition

See Section 4.4.

## 10.9.5. Substudy A Population

### 10.9.5.1. Substudy A Inclusion Criteria

Participants are eligible to be included in Substudy A only if all of the following criteria apply:

| | Substudy A |
|---|---|
| **Age and Sex:** | |
| 1. Male or female participants 65 to 85 years of age at Visit 1 (Day 1).<br>• Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants. | X |
| **Type of Participant and Disease Characteristics:** | |
| 2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures. | X |
| 3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.<br>Note: With the exception of heart disease, which is exclusionary (see exclusion criterion 18), healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.11. | X |
| 4. Male participant who is able to father children and willing to use an acceptable method of contraception as outlined in this protocol for at least 28 days after the last dose of study intervention; or female participant not of childbearing potential; or male participant not able to father children.<br>Note: Female participants of nonchildbearing potential must meet the criteria described in the WOCBP section (Section 10.4.3). | X |
| **Informed Consent:** | |
| 5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. | X |

### 10.9.5.2. Substudy A Exclusion Criteria

Participants are excluded from Substudy A if any of the following criteria apply:

| | Substudy A |
|---|---|
| **Medical Conditions:** | |
| 1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. | X |
| 2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s). | X |
| 3. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination. | X |
| 4. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. | X |
| 5. Women who are pregnant or breastfeeding. | X |
| 6. Allergy to egg proteins (egg or egg products) or chicken proteins. | X |
| **Prior/Concomitant Therapy:** | |
| 7. Any participant who has had significant exposure (someone who was within 6 feet of an infected person for a cumulative total of 15 minutes or more over a 24-hour period) to someone with laboratory-confirmed SARS-CoV-2 infection, COVID-19, or influenza in the past 14 days known prior to Visit 1. | X |
| 8. Any participant who has a SARS-CoV-2 RT-PCR or antigen test in the past 10 days prior to Visit 1 that has not been confirmed as negative. | X |
| 9. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. | X |
| 10. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or planned receipt throughout the study. | X |
| 11. Vaccination with any influenza vaccine within 6 months (175 days) before study intervention administration. | X |
| 12. Any participant who has received or plans to receive a modRNA-platform SARS-CoV-2 vaccine within 60 days of Visit 1. | X |
| **Prior/Concurrent Clinical Study Experience:** | |
| 13. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation. | X |

| | Substudy A |
|---|---|
| **Other Exclusions:** | |
| 14. Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality, or an abnormal C-reactive protein or troponin I value.<br>Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same participant.) Please refer to the laboratory normal ranges (provided separately) for grading scales for abnormalities. | X |
| 15. Screening 12-lead ECG that is consistent with probable or possible myocarditis or pericarditis, or demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF interval >450 msec, complete left bundle branch block, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). | X |
| 16. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members. | X |
| 17. Participation in strenuous or endurance exercise through Visit 3. | X |
| 18. Prior history of heart disease. | X |

## 10.9.6. Substudy A Intervention and Concomitant Therapy

### 10.9.6.1. Study Intervention(s) Administered

Study interventions for Substudy A will include:

| Intervention Name | mIRV | qIRV | QIV | QIV |
|---|---|---|---|---|
| **Type** | Vaccine | Vaccine | Vaccine | Vaccine |
| **Dose Formulation** | modRNA | modRNA | | |
| **Unit Dose Strength(s)** | CCI .3 mL | CCI .3 mL | 0.7 mL | 0.7 mL |
| **Dosage Level(s)** | CCI | CCI | | |
| **Route of Administration** | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection |
| **Use** | Experimental | Experimental | Experimental | Standard of care (to be offered to Phase 1 participants as detailed in Section 10.9.4.1) |
| **IMP or NIMP** | IMP | IMP | IMP | NIMP |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor |

| Intervention Name | mIRV | qIRV | QIV | QIV |
|---|---|---|---|---|
| **Packaging and Labeling** | Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement | Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement | Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement | Study intervention will be provided either as PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement |

mIRVs will be mixed at the site to generate bIRV in the dose-level combinations as shown in Table 5.

#### 10.9.6.1.1. Administration

See Section 6.1.1.

During Substudy A, participants will receive 1 dose of study intervention as randomized at Visit 1 and either Visit 5 or 5A in accordance with the SoA (Section 10.9.1). Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm.

Study intervention at Visit 1 will be administered only by an **unblinded** administrator. Study intervention at Visits 5 and 5A will be administered in an open-label manner.

#### 10.9.6.1.2. Medical Devices

See Section 6.1.2.

#### 10.9.6.1.3. Preparation, Handling, Storage, and Accountability

See Section 6.2.

#### 10.9.6.1.4. Preparation and Dispensing

See Section 6.2.1.

During Substudy A, study intervention will be prepared by qualified unblinded site personnel according to the IP manual or package insert and the study intervention administered in such a way to ensure the participants remain blinded.

### 10.9.6.2. Measures to Minimize Bias: Randomization and Blinding

#### 10.9.6.2.1. Allocation to Study Intervention

See Section 6.3.1.

Allocation of study intervention at Visit 1 in Substudy A will be conducted via IRT. Study intervention allocation at Visits 5 and 5A will be conducted in an open-label manner outside of the IRT based on what each participant received as study intervention at Visit 1 as detailed in Section 10.9.4.

#### 10.9.6.2.2. Blinding of Site Personnel

Substudy A is observer-blinded, such that study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded until participants are unblinded at Visit 5. In particular, the individuals who evaluate participant safety will be blinded. Because there are differences in physical appearance of the study interventions, these will be administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the study intervention container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The study will be unblinded by site staff on an ongoing basis as participants complete Visit 5 to determine if licensed QIV or mIRV may be administered (Section 10.9.8.8.6).

#### 10.9.6.2.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants throughout Substudy A.

#### 10.9.6.2.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be

notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

#### 10.9.6.3. Study Intervention Compliance

See Section 6.4.

#### 10.9.6.4. Dose Modification

Not applicable.

#### 10.9.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

#### 10.9.6.6. Treatment of Overdose

See Section 6.7.

#### 10.9.6.7. Concomitant Therapy

See Section 6.8.

### 10.9.7. Discontinuation of Substudy A Intervention and Participant Discontinuation/Withdrawal

See Section 7.

### 10.9.8. Substudy A Assessments and Procedures

The minimal blood sampling volume for all individual participants in this study is approximately 530 mL prior to expanded enrollment and 280 mL for participants enrolled thereafter. For participants enrolled during expanded enrollment, additional optional whole blood samples of approximately 50 mL at Visits 1, 3, and 4 will be obtained from participants for isolation of PBMCs as detailed in Section 10.9.4.1.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

#### 10.9.8.1. Clinical Safety Laboratory Assessments

Please see Section 8.2.4. Additionally, see Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

#### 10.9.8.2. Efficacy and/or Immunogenicity Assessments

Samples will be collected at time points as specified in Section 10.9, and the following assay run on samples at each of these time points:

- HAI

PBMC samples will be used to describe T-cell responses. Some of the sample may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs for understanding the B-cell, T-cell, and antibody repertoires.

##### 10.9.8.2.1. Biological Samples

See Section 8.1.1.

#### 10.9.8.3. Safety Assessments

See Section 8.2.

#### 10.9.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

#### 10.9.8.5. ECGs

See Section 8.2.7.

#### 10.9.8.6. Stopping Rules

The following stopping rules are in place for Substudy A participants, based on review of AE, ECG, and laboratory data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for all vaccine candidates at all dose levels.
- For all participants already vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur within 4 weeks after administration of mIRV, bIRV, or qIRV at Vaccination 1. The mIRV, bIRV, and qIRV groups will be evaluated for contribution to stopping rules collectively; vaccine candidate dose levels will contribute to stopping rules together.

**Stopping Rule Criteria**:

1. If any participant vaccinated with any IRV (at any dose level) develops:
    - A new ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including:
        - Sustained atrial or ventricular arrhythmias
        - Second-degree Mobitz Type II or worse AV block, new bundle branch block
        - Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis.
    - An abnormal troponin I value that is confirmed abnormal on repeat testing, assessed as related to study intervention by the investigator.
2. If ≥1 participant vaccinated with any IRV (at any dose level) develops confirmed myocarditis or pericarditis.
3. If any participant vaccinated with any IRV (at any dose level) dies.
4. ≥1 participant vaccinated with any IRV experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related by the investigator.
5. ≥2 participants vaccinated with any IRV (at any dose level) develop the same or similar Grade 3 or higher unsolicited AE (including laboratory abnormalities, except lymphocyte count and C-reactive protein), other than myocarditis/pericarditis, assessed as related to study intervention by the investigator. Note that the local reactions, systemic events, and fever specified in Section 8.2.3, reported within 7 days from the day of administration of the study intervention, irrespective whether they are recorded in the e-diary or as AEs, are excluded from this stopping rule.

#### 10.9.8.7. Immunogenicity Assessments

See Section 10.9.8.2.

### 10.9.8.8. Substudy A Procedures

#### 10.9.8.8.1. Screening (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform 12-lead triplicate ECG.
- Perform physical examination, including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample of approximately 20 mL as detailed in the laboratory manual for hematology and chemistry laboratory tests as described in Section 10.2.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prior receipt of any COVID-19 vaccine as described in Section 6.8.
- Record licensed influenza vaccine information, if received during the prior influenza season, as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in Section 8.3.

- Remind the participant to use appropriate contraceptives throughout the study, if applicable.

- The investigator or an authorized designee completes the CRF.

#### 10.9.8.8.2. Visit 1 – Vaccination (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Discuss contraceptive use as described in Section 10.4.

- Record nonstudy vaccinations as described in Section 6.8.

- Review screening laboratory results (hematology and chemistry) and ECG results.

- Perform 12-lead triplicate ECG.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure vital signs, including body temperature, pulse rate, and seated blood pressure.

- Collect a blood sample of approximately 20 mL as detailed in the laboratory manual for hematology and chemistry laboratory tests as described in Section 10.2.

- Ensure that the participant continues to meet all of the inclusion criteria and none of the exclusion criteria.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- Obtain the participant's randomization number and study intervention allocation using the IRT system.

- Collect a blood sample (approximately 50 mL), before administration of study intervention, for immunogenicity assessment.

- If the participant has consented to provide a blood sample for description of cell-mediated immune response, collect a blood sample (approximately 50 mL) for PBMC isolation.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary completion requirement to the participant and assist the participant with downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Record AEs as described in Section 8.3.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.8.11).

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

#### 10.9.8.8.3. Visit 2 – Day 3 Follow-up Visit (After Vaccination) – 2 to 4 Days After Visit 1

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Review laboratory results (hematology and chemistry) and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.9.8.8.11.
- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) must result in further assessments as outlined in Section 10.9.8.8.11.
- Measure vital signs, including body temperature, pulse rate, and seated blood pressure.
- Collect a blood sample of approximately 20 mL as detailed in the laboratory manual for hematology and chemistry tests.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.9.8.8.4. Visit 3 – 1-Week Follow-up Visit (After Vaccination) – 6 to 8 Days After Visit 1

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Review laboratory results (hematology and chemistry) and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.9.8.8.11.
- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) must result in further assessments as outlined in Section 10.9.8.8.11.
- Collect a blood sample of approximately 20 mL as detailed in the laboratory manual for hematology and chemistry tests.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant has consented to provide a blood sample for description of cell-mediated immune response, collect a blood sample (approximately 50 mL) for PBMC isolation.
- Review the participant's reactogenicity e-diary data. If the e-diary collection period is complete:
    - Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
    - Collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device (if the visit is conducted after Day 7).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.9.8.8.5. Visit 4 – 4-Week Follow-up Visit (After Vaccination) – 26 to 30 Days After Visit 1

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Review laboratory results (hematology and chemistry) and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.9.8.8.11.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant has consented to provide a blood sample for description of cell-mediated immune response, collect a blood sample (approximately 50 mL) for PBMC isolation.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- If not already completed, collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

#### 10.9.8.8.6. Visit 5 – 8-Week Follow-up Visit (After Vaccination) – 52 to 60 Days After Visit 1

Before any study-related procedures are performed relating to protocol amendment 2, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant.

If the participant does not consent to administration of Vaccination 2, his or her next visit should be Visit 6.

For participants who received QIV at Visit 1, Visit 5 and 5A procedures may be conducted at the same visit, depending on the timing of these visits relative to implementation of protocol amendment 2, and the availability of mIRV A/B on site.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Unblind the participant's study intervention assignment. If the participant has not previously received licensed QIV at Visit 1:
    - Discuss contraceptive use as described in Section 10.4.
    - Measure the participant's body temperature.
    - Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
    - Administer licensed influenza vaccine to the participant per local guidelines if available or when it becomes available for the season, and record this vaccination in the CRF. This vaccination will be considered Vaccination 2 for these participants.
    - Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- For participants who receive QIV at Visit 5 after implementation of protocol amendment 2:

  - If required, explain the e-diary completion requirement to the participant and assist the participant with downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

  - Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

  - Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

  - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

    - Fever ≥39.0°C (≥102.1°F).

    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

    - Severe pain at the injection site.

    - Any severe systemic event.

  - Record AEs as described in Section 8.3.

  - Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

  - Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.8.11).

  - Schedule an appointment for the participant to return for the next study visit.

  - Remind the participant to bring the e-diary to the next visit.

  - The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

#### 10.9.8.8.7. Visit 5A – Vaccination 2 – 52 to 97 Days After Visit 1

Visit 5A procedures should only be conducted for participants who received QIV at Visit 1, and therefore did not receive QIV at Visit 5.

Before any study-related procedures are performed relating to protocol amendment 2, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of Vaccination 2, his or her next visit should be Visit 6.

- Based on the participant's unblinded vaccination assignment obtained at Visit 5, confirm the participant received QIV at Visit 1.

- Record nonstudy vaccinations as described in Section 6.8.

- Record prohibited medication use as described in Section 6.8.1.

- Discuss contraceptive use as described in Section 10.4.

- Measure the participant's body temperature.

- Ensure that the participant continues to meet all of the inclusion criteria and none of the exclusion criteria.

- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.

- If Visit 5 and 5A procedures are being conducted as separate visits, collect a blood sample of approximately 50 mL for immunogenicity testing.

- Site staff member(s) will dispense/administer either of the following into the deltoid muscle of the preferably nondominant arm:

  - mIRV at a dose level of CCI encoding A strain, or

  - mIRV at a dose level of CCI encoding B strain

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- If required, explain the e-diary completion requirement to the participant and assist the participant with downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Record AEs as described in Section 8.3.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.9.8.8.11).

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

#### 10.9.8.8.8. Visit 5B – 4-Week Post–Vaccination 2 Follow-up Visit – 26 to 45 Days After Visit 5 or 5A

Before any study-related procedures are performed relating to protocol amendment 2, voluntary, written, informed consent (via an ICD addendum) will be obtained from the participant. Each signature on the ICD addendum must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD addendum. A copy of the signed and dated ICD addendum must be given to the participant. If the participant does not consent to administration of Vaccination 2, his or her next visit should be Visit 6.

If the participant does not consent to this visit, his or her next visit should be Visit 6.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- If not already completed, collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.

#### 10.9.8.8.9. Visit 6 – 6-Month Follow-up Telephone Contact – 175 to 189 Days After Last Study Vaccination

- Contact the participant by telephone.
- Record AEs as described in Section 8.3.

- Record nonstudy vaccinations as described in Section 6.8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.9.8.8.10. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.3.2), systemic event (Section 8.2.3.3), or fever (Section 8.2.3.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction (Section 8.2.3.2), systemic event (Section 8.2.3.3), or fever (Section 8.2.3.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.3.2.

- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.3.3.

- Assess other findings associated with the reaction and record this on the AE page of the CRF if appropriate.

- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

#### 10.9.8.8.11. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after study vaccination (Vaccination 1 or 2) must be specifically evaluated by a cardiologist for possible myocarditis or pericarditis. The same applies for any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) or abnormal troponin I level is observed at Visit 2 or 3.

In addition to a clinical evaluation, the following should be performed:

- ECG and

- Measurement of the troponin level

For any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) or abnormal troponin I level is observed at Visit 2 or 3, this should be achieved by repeating the assessments with the central vendor(s).

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or

- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

### 10.9.9. Substudy A Statistical Considerations

See Section 9 for general statistical considerations and phase specifics below.

#### 10.9.9.1. Statistical Hypotheses

There are no statistical hypotheses in Substudy A.

#### 10.9.9.1.1. Estimands

The estimands corresponding to the primary, secondary, and exploratory objectives are described in the table in Section 10.9.3.

#### 10.9.9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment for Phase 1 of the study as all analyses are descriptive in nature.

### 10.9.9.2. Analysis Sets

See Section 9.2 for defined analysis sets.

### 10.9.9.3. Statistical Analyses

The SAP will be developed and finalized for this phase before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

#### 10.9.9.3.1. General Considerations

See Section 9 for general considerations of statistical analyses.

Note that, if a clear HAI result is not obtainable for any strain, neutralizing titers will replace HAI titers as the main immunogenicity endpoint for that strain.

### 10.9.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Safety** | • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions, systemic events, and AEs) for each vaccine group after Vaccinations 1 and 2.<br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (SAEs) for each vaccine group after the last vaccination.<br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (abnormal hematology and chemistry laboratory) for each study vaccine at 2 days and 1 week after Vaccination 1.<br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting grading shifts in hematology and chemistry laboratory assessment between baseline and 2 days, and 1 week, after Vaccination 1.<br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants with new ECG abnormalities at 2 days and 1 week after Vaccination 1. |

#### 10.9.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Secondary immunogenicity** | • HAI GMTs and associated 2-sided 95% CIs will be provided for each strain, by vaccine group, at 1, 4, and 8 weeks after receipt of Vaccination 1.<br>• HAI GMFRs from before Vaccination 1 to 1, 4, and 8 weeks after receipt of Vaccination 1, and associated 2-sided 95% CIs, will be provided for each strain, by vaccine group.<br>• The proportion of participants achieving HAI seroconversion at 1, 4, and 8 weeks after receipt of Vaccination 1, and the proportion of participants with HAI titers ≥1:40 before Vaccination 1 and at 1, 4, and 8 weeks after receipt of Vaccination 1, and associated 2-sided Clopper-Pearson 95% CIs will be provided for each strain.<br>• 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 the proportion of participants with HAI titers ≥1:40 for all strains (targeted by the study vaccine) before Vaccination 1 and at 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 at Visit 1.<br>• 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.<br>• 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. 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. |

### 10.9.9.3.4. Tertiary/Exploratory Endpoint(s)

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Tertiary/ exploratory** | CCI |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | [redacted] CCI [redacted] |

### 10.9.9.3.5. Other Analyses

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) within 4 weeks after a study vaccination (Vaccination 1 or 2) will be summarized and listed by vaccine group.

#### 10.9.9.4. Interim Analyses

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.

#### 10.9.9.5. Sample Size Determination

See Section 9.5.

## 10.10. Appendix 10: Substudy B (Phase 1/2)

### 10.10.1. SoA – Substudy B (Phase 1/2)

| Visit Number | Screening | 201 | 202 | 203 | 204 | 205 | 206 | 207 | 208 |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Screening** | **Vaccination 1** | **1-Week Post–Vaccination 1 Visit[a]** | **Vaccination 2[b]** | **Day 3 Follow-up Visit** | **1-Week Follow-up Visit** | **4-Week Follow-up Visit** | **8-Week Follow-up Visit** | **6-Month Telephone Contact** |
| **Visit Window (Days)** | **0 to 28 Days Before Visit 201** | **Day 1** | **6 to 8 Days** | **19 to 23 Days After Visit 201** | **2 to 4 Days** | **6 to 8 Days** | **26 to 30 Days** | **52 to 60 Days** | **175 to 189 Days** |
| | | | | | ***Visits 204 through 208 to be conducted within the number of days indicated relative to the participant's last study vaccination*** | | | | |
| Obtain informed consent | X | | | | | | | | |
| Assign participant number | X | | | | | | | | |
| Obtain demography and medical history data | X | | | | | | | | |
| Obtain details of medications currently taken | X | | | | | | | | |
| Perform physical examination[c] | X | X | | | | | | | |
| Perform clinical assessment | | X | | | | | | | |
| Measure vital signs (including body temperature) | X | X | | | X | | | | |
| Measure body temperature | | | | X | | | | | |
| Perform 12-lead triplicate ECG | X | X | | | X | | | | |
| Collect blood sample for troponin I laboratory testing | ~2.5 mL | ~2.5 mL | | | ~2.5 mL | | | | |
| Collect prior COVID-19 vaccine information | X | | | | | | | | |
| Collect details of any licensed influenza vaccine received in the prior 12 months | X | | | | | | | | |
| Collect nonstudy vaccine information | X | X | X | X | X | X | X | X | X |
| Confirm eligibility | X | X | | X | | | | | |
| Collect prohibited medication use | | | X | X | X | X | X | X | |
| Review troponin I and ECG results | | X | X | X | | X | | | |
| Perform urine pregnancy test on WOCBP | X | X | | | | | | | |
| Confirm use of contraceptives (if appropriate) | X | X | X | X | X | X | X | | |

| Visit Number | Screening | 201 | 202 | 203 | 204 | 205 | 206 | 207 | 208 |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Screening** | **Vaccination 1** | **1-Week Post–Vaccination 1 Visit[a]** | **Vaccination 2[b]** | **Day 3 Follow-up Visit** | **1-Week Follow-up Visit** | **4-Week Follow-up Visit** | **8-Week Follow-up Visit** | **6-Month Telephone Contact** |
| **Visit Window (Days)** | **0 to 28 Days Before Visit 201** | **Day 1** | **6 to 8 Days** | **19 to 23 Days After Visit 201** | **2 to 4 Days** | **6 to 8 Days** | **26 to 30 Days** | **52 to 60 Days** | **175 to 189 Days** |
| | | | | | ***Visits 204 through 208 to be conducted within the number of days indicated relative to the participant's last study vaccination*** | | | | |
| Obtain randomization number and study intervention allocation | | X | | | | | | | |
| Collect blood sample for immunogenicity assessment | | ~50 mL | | ~50 mL | | ~50 mL | ~50 mL | ~50 mL | |
| Collect blood sample for cell-mediated immunogenicity assessment[d] | | ~50 mL | ~ 50 mL | | | ~50 mL | ~50 mL | | |
| Administer study intervention | | X | | X | | | | | |
| Assess acute reactions for at least 30 minutes after study intervention administration | | X | | X | | | | | |
| Explain to the participant e-diary completion requirements and assist the participant with downloading the app or issue provisioned device if required | | X | | | | | | | |
| Provide thermometer and measuring device | | X | | | | | | | |
| Review reactogenicity e-diary data (daily review is optimal during the active diary period) | | ← | → | ← | | | → | | |
| Review ongoing reactogenicity e-diary symptoms and obtain stop dates | | | X | X | | X | X | | |

| Visit Number | Screening | 201 | 202 | 203 | 204 | 205 | 206 | 207 | 208 |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Description** | **Screening** | **Vaccination 1** | **1-Week Post–Vaccination 1 Visit[a]** | **Vaccination 2[b]** | **Day 3 Follow-up Visit** | **1-Week Follow-up Visit** | **4-Week Follow-up Visit** | **8-Week Follow-up Visit** | **6-Month Telephone Contact** |
| **Visit Window (Days)** | **0 to 28 Days Before Visit 201** | **Day 1** | **6 to 8 Days** | **19 to 23 Days After Visit 201** | **2 to 4 Days** | **6 to 8 Days** | **26 to 30 Days** | **52 to 60 Days** | **175 to 189 Days** |
| | | | | | ***Visits 204 through 208 to be conducted within the number of days indicated relative to the participant's last study vaccination*** | | | | |
| Collect AEs and SAEs as appropriate | X | X | X | X | X | X | X[e] | X[e] | X |
| Collect e-diary or assist the participant with deleting application | | | | | | X[f] | X | | |

Abbreviations: COVID-19 = coronavirus disease 2019; ECG = electrocardiography.

a. Visit 202 is to be conducted during initial enrollment for participants assigned to a 2-visit vaccination schedule only.
b. Vaccination 2 (Visit 203) is only conducted for participants randomized to receive a 2-visit vaccination schedule.
c. Physical examination at Visit 201 will be conducted if clinically indicated.
d. Additional 50 mL for cell-mediated immunogenicity assessments as detailed in Section 10.10.4.
e. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3).
f. If Visit 205 is conducted after Day 7.

### 10.10.2. Introduction

#### 10.10.2.1. Substudy Rationale

Substudy B is a Phase 1/2 randomized, single-blind (sponsor-unblinded) substudy to evaluate the safety and immunogenicity of the following vaccination schedules:

In participants 65 to 85 years of age:

- 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 followed by a dose of bIRV encoding 2 A strains at a dose level of either CCI, administered 21 days apart.
- 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).

In participants 18 to 64 years of age:

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

#### 10.10.2.2. Background

See Section 2.2.

#### 10.10.2.3. Benefit/Risk Assessment

Benefits to individual participants enrolled in Substudy B may be:

- Contributing to research to help others.

Please see Section 2.3.3 for details of the SRSDs relating to the study intervention used in Substudy B.

### 10.10.3. Objectives, Endpoints, and Estimands (Substudy B)

For the purposes of the study 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.

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary Safety:** | **Primary Safety:** | **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:<br>• Local reactions for up to 7 days following each vaccination<br>• Systemic events for up to 7 days following each vaccination<br>• AEs from the first vaccination to 4 weeks after the last vaccination<br>• SAEs from the first vaccination to 6 months after the last vaccination | • Local reactions (pain at the injection site, redness, and swelling)<br>• Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)<br>• AEs<br>• SAEs |
| | The percentage of participants with:<br>• Abnormal troponin I laboratory values 2 days after the last vaccination | Troponin I laboratory parameters detailed in Section 10.2 |
| | The percentage of participants with:<br>• New ECG abnormalities 2 days after the last vaccination | ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in Section 8.2.7 |
| **Secondary:** | **Secondary:** | **Secondary:** |
| 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:<br>• 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<br>• 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<br>• 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 | HAI titers for each strain targeted by the study vaccine |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | • 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 | |
| | In participants having 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:<br>• 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<br>• 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:<br>• HAI GMTs before vaccination and at 1, 4, and 8 weeks after receipt of vaccination<br>• HAI GMFR from before vaccination to 1, 4, and 8 weeks after receipt of vaccination<br>• The proportion of participants achieving HAI seroconversion for each strain at 1, 4, and 8 weeks after receipt of vaccination<br>• 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<br>• The proportion of participants achieving HAI seroconversion for all strains at 1, 4, and 8 weeks after receipt of vaccination<br>• 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 |

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Tertiary/Exploratory:** | **Tertiary/Exploratory:** | **Tertiary/Exploratory:** |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

### 10.10.4. Substudy B Design

#### 10.10.4.1. Overall Design

This is a randomized, single-blinded (sponsor-unblinded) substudy to evaluate the safety and immunogenicity of the vaccination schedules detailed below. The design of Substudy B is summarized in Section 1.2.2.

Participants 65 to 85 years of age will be randomized to one of the following vaccination schedules at Visit 201 (Vaccination 1) 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).

It is anticipated that the following strains will be used in the bIRV, but the final strain selection will be detailed in the IP manual: CCI It is anticipated that the following strains will be used in the qIRV, but the final strain selection will be detailed in the IP manual: CCI

The strains used in qIRV may vary depending on the time of enrollment relative to the annual influenza season.

Substudy B enrollment of participants 65 to 85 years of age will be separated into an initial and expanded enrollment. Depending on the availability of study intervention and operational prioritization, groups of participants 65 to 85 years of age in Substudy B may not all be randomized concurrently; however, a minimum of 2 groups will be open for randomization at any one time. Participants 18 to 64 years of age will only be included in the study during expanded enrollment: 240 participants 18 to 64 years of age will be randomized 1:1 to receive either a single dose of CCI qIRV (encoding 2 A strains and 2 B strains at a dose level of CCI ) or a single dose of CCI qIRV (encoding 2 A strains and 2 B strains at a dose level of CCI ).

During initial enrollment (participants 65 to 85 years of age):

- Each group (vaccine formulation/dose level, or control) will comprise 15 participants. Hence, Substudy B initial enrollment will comprise approximately 90 participants.

- Enrollment will be controlled for the first group in which the total dose of modRNA vaccine administered at a single vaccination is CCI, and also for the first group in which the total dose is CCI as follows:

  - No more than 5 participants can be vaccinated on the first day.

  - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination.

- Safety and immunogenicity data accumulated at least 1 week following the last vaccination in each group will be reviewed by the sponsor's IRC and, if deemed acceptable, an additional 120 participants 65 to 85 years of age will be enrolled in that group (expanded enrollment).

- If a group is not selected for enrollment expansion or, based on review of immunogenicity data at the 4-week time point, at the sponsor's discretion, subsequent collection of blood samples from participants in that group may be halted and/or not analyzed.

As detailed above, 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. Additionally,

- 240 participants 18 to 64 years of age will be randomized 1:1 to receive either a single dose of CCI qIRV (encoding 2 A strains and 2 B strains at a dose level of CCI ) or a single dose of CCI qIRV (encoding 2 A strains and 2 B strains at a dose level of CCI ).

- 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].

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

Therefore, Substudy B expanded enrollment will consist of approximately 120 to 1725 participants, depending on the number of groups selected to progress to expanded enrollment.

Stopping rules will apply throughout initial and expanded enrollment as detailed in Section 10.10.8.6.

All participants will be asked to complete a reactogenicity e-diary for 7 days following each vaccination. Blood samples of approximately 50 mL will be collected for immunogenicity assessments prior to Vaccination 1, prior to Vaccination 2 (if applicable), and at 1, 4, and 8 weeks after the participant's last vaccination.

The total duration of the study for each participant will be up to approximately 8 months.

All participants will be asked to provide an additional blood sample of approximately 2.5 mL at time points specified in Section 10.10.1 for assessment of troponin I.

All participants enrolled prior to expanded enrollment will be asked to provide an additional blood sample of 50 mL at time points specified in Section 10.10.1 for assessment of cell-mediated immunogenicity.

During expanded enrollment, all or a subset of participants will be asked to provide an additional optional blood sample of 50 mL at time points specified in Section 10.10.1 for assessment of cell-mediated immunogenicity. The number of participants asked to provide these samples will be determined by Pfizer, contingent on operational considerations.

#### 10.10.4.2. Scientific Rationale for Study Design

See Section 2.1.

#### 10.10.4.3. Justification for Dose

See Section 4.3.

#### 10.10.4.4. End of Study Definition

See Section 4.4.

### 10.10.5. Substudy B Population

#### 10.10.5.1. Substudy B Inclusion Criteria

Participants are eligible to be included in Substudy B only if all of the following criteria apply:

| | Substudy B |
|---|---|
| **Age and Sex:** | |
| 1. During enrollment of Groups 1 to 12 (Table 6): male or female participants 65 to 85 years of age at Visit 201 (Day 1) or,<br><br>During enrollment of Groups 13 and 14 (Table 6): male or female participants 18 to 64 years of age at Visit 201 (Day 1).<br><br>• Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants. | X |
| **Type of Participant and Disease Characteristics:** | |
| 2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures. | X |
| 3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.<br><br>Note: With the exception of heart disease, which is exclusionary (see exclusion criterion 16), healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.11. | X |
| 4. For participants 65 to 85 years of age at the time of enrollment, receipt of licensed influenza vaccination for the 2021-2022 northern hemisphere season >4 months (120 days) before study intervention administration. | X |
| **Informed Consent:** | |
| 5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. | X |

### 10.10.5.2. Substudy B Exclusion Criteria

Participants are excluded from Substudy B if any of the following criteria apply:

| | Substudy B |
|---|---|
| **Medical Conditions:** | |
| 1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. | X |
| 2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s). | X |
| 3. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination. | X |
| 4. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. | X |
| 5. Women who are pregnant or breastfeeding. | X |
| 6. Allergy to egg proteins (egg or egg products) or chicken proteins. | X |
| **Prior/Concomitant Therapy:** | |
| 7. Any participant who has had significant exposure (someone who was within 6 feet of an infected person for a cumulative total of 15 minutes or more over a 24-hour period) to someone with laboratory-confirmed SARS-CoV-2 infection, COVID-19, or influenza in the past 14 days known prior to Visit 201. | X |
| 8. Any participant who has a SARS-CoV-2 RT-PCR or antigen test in the past 10 days prior to Visit 201 that has not been confirmed as negative. | X |
| 9. Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. | X |
| 10. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or planned receipt throughout the study. | X |
| 11. Any participant who has received or plans to receive a modRNA-platform SARS-CoV-2 vaccine within 28 days of Visit 201. | X |
| 12. Any participant who has received licensed influenza vaccination for the 2022-2023 northern hemisphere influenza season. | X |
| **Prior/Concurrent Clinical Study Experience:** | |
| 13. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation. | X |

| | Substudy B |
|---|---|
| **Other Exclusions:** | |
| 14. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members. | X |
| 15. Participation in strenuous or endurance exercise through Visit 205. | X |
| 16. Prior history of heart disease. | X |
| 17. Any abnormal screening troponin I laboratory value. | X |
| 18. Screening 12-lead ECG that, as judged by the investigator, is consistent with probable or possible myocarditis or pericarditis, or demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results. Participants with a screening 12-lead ECG that shows an average QTcF interval >450 msec, complete left bundle branch block, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias should be excluded from study participation. | X |

## 10.10.6. Substudy B Intervention and Concomitant Therapy

### 10.10.6.1. Study Intervention(s) Administered

Study interventions for Substudy B will include:

| Intervention Name | mIRV | qIRV | QIV | Normal Saline Placebo |
|---|---|---|---|---|
| **Type** | Vaccine | Vaccine | Vaccine | Placebo |
| **Dose Formulation** | modRNA | modRNA | | Normal saline (0.9% sodium chloride solution for injection) |
| **Unit Dose Strength(s)** | CCI 0.3 mL | CCI 0.3 mL | 0.7 mL | |
| **Dosage Level(s)** | CCI | CCI | | N/A |
| **Route of Administration** | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection |
| **Use** | Experimental | Experimental | Experimental | Placebo for expanded enrollment |
| **IMP or NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor |

| Intervention Name | mIRV | qIRV | QIV | Normal Saline Placebo |
|---|---|---|---|---|
| **Packaging and Labeling** | Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement | Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement | Study intervention will be provided either as a PFS or in a glass vial as open-label supply. Each PFS/vial will be labeled as required per country requirement | Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement |

mIRVs encoding HA for each A and B strain will be mixed at the site to generate either bIRV at a dose level of either CCI, or qIRV at dose level combinations other than CCI. Please see the IP manual for further details.

### 10.10.6.1.1. Administration

See Section 6.1.1.

During Substudy B, participants will receive study intervention as randomized at Visit 201 and, if applicable, at Visit 203 in accordance with the SoA (Section 10.10.1).

Study intervention should be administered intramuscularly as detailed in Table 6.

**Table 6. Substudy B Study Intervention Schedule**

| Participant Age | Vaccine Group | Study Intervention - Vaccination 1 | | Study Intervention - Vaccination 2 | |
|---|---|---|---|---|---|
| | | Right Deltoid[a] | Left Deltoid | Right Deltoid[a] | Left Deltoid |
| 65 to 85 years of age | 1 | qIRV CCI 2 x A, 2 x B CCI | | qIRV CCI 2 x A, 2 x B CCI | |
| | 2 | Licensed QIV | | bIRV CCI 2 x A CCI | |
| | 3 | Licensed QIV | | bIRV CCI 2 x A CCI | |
| | 4 | Licensed QIV | | Licensed QIV | |
| | 5 | bIRV CCI 2 x A CCI | Licensed QIV | | |
| | 6 | bIRV CCI 2 x A CCI | Licensed QIV | | |
| | 7 | qIRV CCI 2 x A, 2 x B CCI | | | |
| | 8 | Licensed QIV | | | |
| | 9 | bIRV CCI 2 x B CCI | bIRV CCI 2 x A CCI | | |
| | 10 | qIRV CCI 2 x A CCI 2 x B CCI | | | |

**Table 6. Substudy B Study Intervention Schedule**

| Participant Age | Vaccine Group | Study Intervention - Vaccination 1 | | Study Intervention - Vaccination 2 | |
|---|---|---|---|---|---|
| | | Right Deltoid[a] | Left Deltoid | Right Deltoid[a] | Left Deltoid |
| 18 to 64 years of age | 11 | qIRV CCI 2 x A CCI 2 x B CCI | | | |
| | 12 | Licensed QIV | | | Placebo |
| | 13 | qIRV CCI 2 x A, 2 x B CCI | | | |
| | 14 | qIRV CCI 2 x A, 2 x B CCI | | | |

a. Local reactions will be assessed at the injection site on the right deltoid (see Section 8.2.3.2).

Study intervention in Substudy B will be administered in a single-blinded manner.

#### 10.10.6.1.2. Medical Devices

See Section 6.1.2.

#### 10.10.6.1.3. Preparation, Handling, Storage, and Accountability

See Section 6.2.

#### 10.10.6.1.4. Preparation and Dispensing

See Section 6.2.1.

During Substudy B, study intervention will be prepared by qualified site personnel according to the IP manual or package insert and the study intervention administered in such a way to ensure that the participants remain blinded.

### 10.10.6.2. Measures to Minimize Bias: Randomization and Blinding

#### 10.10.6.2.1. Allocation to Study Intervention

See Section 6.3.1.

Allocation of study intervention at Visit 201 in Substudy B will be conducted via IRT.

#### 10.10.6.2.2. Blinding of Site Personnel

Substudy B is single-blinded, such that all site personnel, including the investigator, investigator staff, and study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. Study participants, however, will remain blinded to which 1- or 2-visit vaccination schedule they receive (see Section 10.10.4.1).

#### 10.10.6.2.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants throughout Substudy B.

#### 10.10.6.2.4. Breaking the Blind

Not applicable.

### 10.10.6.3. Study Intervention Compliance

See Section 6.4.

### 10.10.6.4. Dose Modification

Not applicable.

### 10.10.6.5. Continued Access to Study Intervention After the End of the Study

See Section 6.6.

### 10.10.6.6. Treatment of Overdose

See Section 6.7.

### 10.10.6.7. Concomitant Therapy

See Section 6.8.

## 10.10.7. Discontinuation of Substudy B Intervention and Participant Discontinuation/Withdrawal

See Section 7.

## 10.10.8. Substudy B Assessments and Procedures

The minimal blood sampling volume for all individual participants in this study is approximately 457.5 mL prior to expanded enrollment and 257.5 mL for participants enrolled thereafter. For participants enrolled during expanded enrollment, additional optional whole blood samples of approximately 50 mL at Visits 201, 202, 205, and 206 will be obtained from participants for isolation of PBMCs as detailed in Section 10.10.4.1.

For all participants, other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

#### 10.10.8.1. Clinical Safety Laboratory Assessments

Please see Section 8.2.4. Additionally, see Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

#### 10.10.8.2. Efficacy and/or Immunogenicity Assessments

Samples will be collected at time points as specified in Section 10.10.1, and the following assay will be run on samples at each of these time points:

- HAI

PBMC samples will be used to describe T-cell responses. Some of the samples may be used for sequencing of participants' antibody and/or BCR heavy- and light-chain genes, TCR genes, and/or mRNAs for understanding the B-cell, T-cell, and antibody repertoires.

##### 10.10.8.2.1. Biological Samples

See Section 8.1.1.

#### 10.10.8.3. Safety Assessments

See Section 8.2.

Note, for Substudy B, local reactions will be assessed at the injection site on the right arm only (see Section 8.2.3.2).

#### 10.10.8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

See Section 8.3.

#### 10.10.8.5. ECGs

See Section 8.2.7.

#### 10.10.8.6. Stopping Rules

The following stopping rules are in place for Substudy B participants, based on review of AE, ECG, and laboratory data. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded, so they will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.

- The stopping rule will PAUSE randomization and study intervention administration for all vaccine candidates at the affected and, if applicable, higher total dose level CCI , eg, if a stopping rule is met in a group receiving study intervention at a total dose of CCI , this will pause randomization and study intervention administration in all groups receiving study intervention at a total dose level of CCI .

- For all participants already vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur within 4 weeks after administration of any IRV at Vaccination 1 or 2. Each IRV dose level will be evaluated for contribution to stopping rules independently.

**Stopping Rule Criteria:**

1. If any participant vaccinated with any IRV develops:

    - A new ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including:

        - Sustained atrial or ventricular arrhythmias

        - Second-degree Mobitz Type II or worse AV block, new bundle branch block

        - Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis

    - An abnormal troponin I value that is confirmed abnormal on repeat testing, assessed as related to study intervention by the investigator.

2. If ≥1 participant vaccinated with any IRV develops confirmed myocarditis or pericarditis.

3. If any participant vaccinated with any IRV dies.

4. If ≥1 participant vaccinated with any IRV experiences a Grade 4 unsolicited AE, or SAE of any severity, assessed as related by the investigator.

5. If ≥2 participants vaccinated with any IRV at the same dose level develop the same or similar Grade 3 or higher unsolicited AE, other than myocarditis/pericarditis, assessed as related to study intervention by the investigator. Note that the local reactions, systemic events, and fever specified in Section 8.2.3, reported within 7 days from the day of administration of the study intervention, irrespective of whether they are recorded in the e-diary or as AEs, are excluded from this stopping rule.

### 10.10.8.7. Immunogenicity Assessments

See Section 10.10.8.2.

### 10.10.8.8. Substudy B Procedures

#### 10.10.8.8.1. Screening (0 to 28 Days Before Visit 201)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform 12-lead triplicate ECG.
- Perform physical examination, including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 10.2.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prior receipt of any COVID-19 vaccine as described in Section 6.8.
- Record details of any licensed influenza vaccine received in the prior 12 months, as described in Section 6.8.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Record AEs as described in Section 8.3.
- Remind the participant to use appropriate contraceptives throughout the study, if applicable.
- The investigator or an authorized designee completes the CRF.

#### 10.10.8.8.2. Visit 201 – Vaccination 1 (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.8.
- Review screening laboratory troponin I and ECG results.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Perform 12-lead triplicate ECG.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 10.2.
- Measure vital signs, including body temperature, pulse rate, and seated blood pressure.
- Perform urine pregnancy test on WOCBP as described in Section 8.2.5.
- Ensure that the participant continues to meet all of the inclusion criteria and none of the exclusion criteria.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- Collect a blood sample (approximately 50 mL), before administration of study intervention, for immunogenicity assessment.

- If the participant has consented to provide a blood sample for description of cell-mediated immune response, collect a blood sample (approximately 50 mL) for PBMC isolation.

- Site staff member(s) will dispense/administer study intervention, depending on the allocated study intervention/vaccine schedule, as detailed in Table 6. Please refer to the IP manual for further instruction on this process.

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

- Explain the e-diary completion requirement to the participant and assist the participant with downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Record AEs as described in Section 8.3.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.8.11).

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.
- Complete the CRFs and study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

#### 10.10.8.8.3. Visit 202 – 1-Week Post–Vaccination 1 Visit – 6 to 8 Days After Vaccination 1

Visit 202 is to be conducted during initial enrollment for participants assigned to 2-visit vaccination schedules only.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Review troponin I laboratory and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.10.8.8.11.
- Collect a blood sample (approximately 50 mL) for PBMC isolation.
- Review the participant's reactogenicity e-diary data. If the e-diary collection period is complete, collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.10.8.8.4. Visit 203 – Vaccination 2 – 19 to 23 Days After Visit 201

Vaccination 2 (Visit 203) should only be conducted for participants randomized to 2-visit vaccination schedules.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review troponin I and ECG results.
- Discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety and immunogenicity (see Section 7.1).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Collect a blood sample (approximately 50 mL), before administration of study intervention, for immunogenicity assessment.
- Site staff member(s) will dispense/administer study intervention, depending on the allocated study intervention/vaccine schedule, as detailed in Table 6. Please refer to the IP manual for further instruction on this process.

- Site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.

- Ensure the participant remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

  - Fever ≥39.0°C (≥102.1°F).

  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).

  - Severe pain at the injection site.

  - Any severe systemic event.

- Record AEs as described in Section 8.3.

- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.8.11).

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant to bring the e-diary to the next visit.

- Complete the source documents.

- Complete the CRFs and study intervention accountability records.

- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

#### 10.10.8.8.5. Visit 204 – Day 3 Follow-up Visit (After Vaccination 1 or 2) – 2 to 4 Days After Last Study Vaccination

Visit 204 is to be conducted within 2 to 4 days after Visit 201 or 203, depending on if the participant is assigned to a 1- or 2-visit vaccination schedule.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Perform 12-lead triplicate ECG. Any new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) must result in further assessments as outlined in Section 10.10.8.8.11.
- Measure vital signs, including body temperature, pulse rate, and seated blood pressure.
- Collect a blood sample of approximately 2.5 mL as detailed in the laboratory manual for troponin I laboratory testing as described in Section 10.2.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
  - Severe pain at the injection site.
  - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.10.8.8.6. Visit 205 – 1-Week Follow-up Visit (After Vaccination 1 or 2) – 6 to 8 Days After Last Study Vaccination

Visit 205 is to be conducted within 6 to 8 days after Visit 201 or 203, depending on if the participant is assigned to a 1- or 2-visit vaccination schedule.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Review troponin I laboratory and ECG results. Any abnormal troponin I level must result in further assessments as outlined in Section 10.10.8.8.11.
- Collect a blood sample of approximately 50 mL for immunogenicity testing.
- If the participant has consented to provide a blood sample for description of cell-mediated immune response, collect a blood sample (approximately 50 mL) for PBMC isolation.
- Review the participant's reactogenicity e-diary data. If the e-diary collection period is complete:
    - Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
    - Collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device (if the visit is conducted after Day 7).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
    - Fever ≥39.0°C (≥102.1°F).
    - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
    - Severe pain at the injection site.
    - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.

- Ask the participant to contact the site staff or investigator if the participant experiences acute chest pain, shortness of breath, or palpitations (see Section 10.10.8.8.11).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.10.8.8.7. Visit 206 – 4-Week Follow-up Visit (After Vaccination 1 or 2) – 26 to 30 Days After Last Study Vaccination

Visit 206 is to be conducted within 26 to 30 days after Visit 201 or 203, depending on if the participant is assigned to a 1- or 2-visit vaccination schedule.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Discuss contraceptive use as described in Section 10.4.
- Collect a blood sample of approximately 50 mL for immunogenicity testing, unless advised otherwise by the sponsor based on the vaccine group to which the participant is assigned.
- If the participant has consented to provide a blood sample for description of cell-mediated immune response, collect a blood sample (approximately 50 mL) for PBMC isolation, unless advised otherwise by the sponsor based on the vaccine group to which the participant is assigned.
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- If not already completed, collect the participant's e-diary or assist the participant with removing the study application from his or her own personal device.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

#### 10.10.8.8.8. Visit 207 – 8-Week Follow-up Visit (After Vaccination 1 or 2) – 52 to 60 Days After Last Study Vaccination

Visit 207 is to be conducted within 52 to 60 days after Visit 201 or 203, depending on if the participant is assigned to a 1- or 2-visit vaccination schedule.

- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Record prohibited medication use as described in Section 6.8.1.
- Collect a blood sample of approximately 50 mL for immunogenicity testing, unless advised otherwise by the sponsor based on the vaccine group to which the participant is assigned.
- Record any AEs that occur within the 48 hours after the blood draw as described in Section 8.3.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.10.8.8.9. Visit 208 – 6-Month Follow-up Telephone Contact – 175 to 189 Days After Last Study Vaccination

Visit 208 is to be conducted within 175 to 189 days after Visit 201 or 203, depending on if the participant is assigned to a 1- or 2-visit vaccination schedule.

- Contact the participant by telephone.
- Record AEs as described in Section 8.3.
- Record nonstudy vaccinations as described in Section 6.8.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

#### 10.10.8.8.10. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.3.2), systemic event (Section 8.2.3.3), or fever (Section 8.2.3.4) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If a suspected Grade 4 local reaction (Section 8.2.3.2), systemic event (Section 8.2.3.3), or fever (Section 8.2.3.4) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets Grade 4 criteria.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.3.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.2.3.3.
- Assess other findings associated with the reaction and record this on the AE page of the CRF if appropriate.

- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

#### 10.10.8.8.11. Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after study vaccination (Vaccination 1 or 2) must be specifically evaluated by a cardiologist for possible myocarditis or pericarditis. The same applies for any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) or abnormal troponin I level is observed at Visit 202 or 204.

In addition to a clinical evaluation, the following should be performed:

- ECG and
- Measurement of the troponin level

For any participant in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis (as listed in Section 8.2.7) or abnormal troponin I level is observed at Visit 202 or 204, this should be achieved by repeating the assessments with the central vendor(s).

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Details of the symptoms reported, and results of the investigations performed, will be recorded in the CRF.

### 10.10.9. Substudy B Statistical Considerations

See Section 9 for general statistical considerations and phase specifics below.

#### 10.10.9.1. Statistical Hypotheses

There are no statistical hypotheses in Substudy B.

#### 10.10.9.1.1. Estimands

The estimands corresponding to the primary, secondary, and exploratory objectives are described in the table in Section 10.10.3.

#### 10.10.9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment for Substudy B as all analyses are descriptive in nature.

### 10.10.9.2. Analysis Sets

See Section 9.2 for defined analysis sets.

### 10.10.9.3. Statistical Analyses

The SAP will be developed and finalized for this phase before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

#### 10.10.9.3.1. General Considerations

See Section 9 for general considerations of statistical analyses.

Note that, if a clear HAI result is not obtainable for any strain, neutralizing titers will replace HAI titers as the main immunogenicity endpoint for that strain.

### 10.10.9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Safety** (adults 65 to 85 years of age) | • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions and systemic events) for each vaccine group for up to 7 days following each vaccination.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each AE from the first vaccination to 4 weeks after the last vaccination, by vaccination group.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each SAE from the first vaccination to 6 months after the last vaccination, by vaccination group.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting abnormal troponin I levels for each study vaccine at 2 days after the last vaccination.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants with new ECG abnormalities at 2 days after the last vaccination. |

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Safety** (adults 18 to 64 years of age) | • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions and systemic events) for up to 7 days after vaccination.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each AE from the first vaccination to 4 weeks after vaccination.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each SAE from the first vaccination to 6 months after vaccination.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting abnormal troponin I levels at 2 days after vaccination.<br><br>• Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants with new ECG abnormalities at 2 days after vaccination. |

### 10.10.9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Secondary immunogenicity** (adults 65 to 85 years of age) | • HAI GMTs and associated 2-sided 95% CIs will be provided for each strain, by vaccine group, before Vaccination 1 and prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination.<br>• HAI GMFRs from before Vaccination 1 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 for each strain, by vaccine group.<br>• The proportion of participants achieving HAI seroconversion prior to Vaccination 2 (Day 21, if applicable) and at 1, 4, and 8 weeks after receipt of the last vaccination, and the proportion of participants with HAI titers ≥1:40 before Vaccination 1 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 each strain.<br>• 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 the proportion of participants with HAI titers ≥1:40 for all strains (targeted by the study vaccine) before Vaccinations 1 and 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. |
| **Secondary immunogenicity** (adults 18 to 64 years of age) | • HAI GMTs and associated 2-sided 95% CIs will be provided for each strain before vaccination and at 1, 4, and 8 weeks after receipt of vaccination.<br>• HAI GMFRs from before vaccination to 1, 4, and 8 weeks after receipt of vaccination, and associated 2-sided 95% CIs, will be provided for each strain.<br>• The proportion of participants achieving HAI seroconversion at 1, 4, and 8 weeks after receipt of vaccination, and the proportion of participants with HAI titers ≥1:40 before vaccination and at 1, 4, and 8 weeks after receipt of the vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be provided for each strain.<br>• 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, and the proportion of participants with HAI titers ≥1:40 for all strains (targeted by the study vaccine) before vaccination and at 1, 4, and 8 weeks after receipt of vaccination, and associated 2-sided Clopper-Pearson 95% CIs, will be provided. |

### 10.10.9.3.4. Tertiary/Exploratory Endpoint(s)

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Tertiary/ exploratory** (adults 65 to 85 years of age) | CCI |
| **Tertiary/ exploratory** (adults 18 to 64 years of age) | CCI |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | [redacted] CCI [redacted] |

### 10.10.9.3.5. Other Analyses

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis (ECG, troponin level, cardiac echocardiogram, and/or cardiac magnetic resonance study) within 4 weeks after a study vaccination (Vaccination 1 or 2) will be summarized and listed by vaccine group.

### 10.10.9.4. Interim Analyses

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.

### 10.10.9.5. Sample Size Determination

See Section 9.5.

## 10.11. Appendix 11: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/$mm^3$ within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation

## 10.12. Appendix 12: Genetics

### Use/Analysis of DNA and/or RNA

- Genetic variation may impact a participant's response to study intervention as well as susceptibility to and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for PBMC isolation and may be used for DNA and/or RNA analysis.

- The results of genetic analyses may be reported in a CSR or in a separate study summary, or may be used for internal decision-making without being included in a study report.

- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.5) will be stored for up to 15 years or other period as per local requirements.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

## 10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

**Amendment 4 (08 February 2022)**

**Overall Rationale for the Amendment:**

Addition of further groups to Substudy B to describe the safety and immunogenicity of the following vaccination schedules:

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

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | Updated the number of participants. | To reflect additional randomization groups added to Substudy B. |
| 1.2.2 Substudy B (Phase 1/2) Schema | Updated the schema to include additional randomization groups. | Additional groups added to the Substudy B design. |
| 2.1 Study Rationale | Added a description of additional Substudy B randomization groups. | Additional groups added to the Substudy B design. |
| 2.3.1 Risk Assessment | Added qIRV and a reference to CCI to the requirement for stepwise enrollment. | Risk mitigation when dosing participants with CCI modRNA. |
| 9.2 Analysis Sets | Updated the definition of the safety population in line with the SAP. | Correct an error. |
| 9.5 Sample Size Determination | Updated text to reflect the new study sample size. | Additional groups added to the Substudy B design. |
| 10.9.3 Objectives, Endpoints, and Estimands (Substudy A) | Removed the microneutralization objective and estimands. Removed microneutralization as a replacement for HAI if clear HAI results are not obtainable.<br><br>Applied corresponding updates to Substudy B and made updates in Sections 10.9.8.2, 10.9.9.3.4, 10.10.3, 10.10.8.2, and 10.10.9.3.4. | A validated microneutralization assay may not be available for the time of study reporting. Although such testing may be conducted in the future, these exploratory estimands have been removed from the protocol for clarity. Removal of microneutralization as a replacement for HAI is warranted based on experience to-date from HAI assays used in this study. |
| 10.10.2.1 Substudy Rationale | Added a description of additional Substudy B randomization groups. | Additional groups added to the Substudy B design. |
| 10.10.4.1 Overall Design | Added a description of additional Substudy B randomization groups, and associated details, eg, nonconcurrent randomization. | Additional groups added to the Substudy B design. |
| 10.10.6.1 Study Intervention(s) Administered | Updated text to confirm that qIRV doses other than 7CCI will be generated on site by mixing of mIRVs. | Additional qIRV groups added to the Substudy B design. |
| 10.10.6.1.1 Administration | Added Table 6 detailing the Substudy B study intervention schedule. | Additional groups added to the Substudy B design – study intervention is to be administered in specific arms to ensure accurate assessment of local reactions. |
| 10.10.8.8.7 4-Week Follow-up Visit; and 10.10.8.8.8 8-Week Follow-up Visit | Clarified that blood sample collection may be halted at the discretion of the sponsor, consistent with Section 10.10.4.1. | For consistency with existing wording in Section 10.10.4.1. |

**Amendment 3 (13 January 2022)**

**Overall Rationale for the Amendment:**

Addition of Phase 1/2 Substudy B to describe the safety and immunogenicity of the following vaccination schedules:

- 2 Doses of qIRV encoding 2 A strains and 2 B strains at a dose level of CCI [redacted], administered 21 days apart,
- 2 Doses of licensed QIV, administered 21 days apart (as a control group),
- A dose of licensed QIV followed by a dose of bIRV encoding 2 A strains at a dose level of either CCI [redacted], administered 21 days apart, and
- A dose of licensed QIV administered concurrently in the opposite arm with bIRV encoding 2 A strains at a dose level of either CCI [redacted].

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2.1 Substudy A (Phase 1) Schema | Removed expanded enrollment from Substudy A. | Based upon preliminary immunogenicity data, the sponsor decided not to expand enrollment into Substudy A. |
| 1.2.2 Substudy B (Phase 1/2) Schema | Schema included to match the addition of Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 2.1 Study Rationale | Rationale for Substudy B added. | Addition of Substudy B in protocol amendment 3. |
| 2.3.1 Risk Assessment | Added risks associated with vaccine groups in Substudy B. | Addition of Substudy B in protocol amendment 3, which includes vaccine groups with a total dose of bIRV CCI [redacted], and groups with a previously undefined safety profile. |
| 4.1 Overall Design | Detailed overall design moved to under Substudy A and B as appropriate. | To document reorganization for clarity, and to reduce repetition. |
| 4.3 Justification for Dose | Justification added for 2-dose vaccine groups and those containing a total dose of bIRV CCI [redacted]. | To support addition of Substudy B in protocol amendment 3, which includes vaccine groups with a total dose of bIRV CCI [redacted], and groups with a previously undefined safety profile. |
| 5.1 Inclusion Criteria, and 5.2. Exclusion Criteria | Inclusion/exclusion criteria moved to under Substudy A and B as appropriate. | To document reorganization for clarity. |
| 6.8 Concomitant Therapy | Added details regarding prior influenza vaccine receipt for Substudy B, and other updates to accommodate Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 6.8.1 Prohibited During the Study | Updated the criterion for receipt of mRNA-platform SARS-CoV-2 vaccine. | To clarify that this criterion only applies to modRNA-containing study vaccinations, and that the window for Substudy B differs from that for Substudy A. |
| 8.2.1 Physical Examinations | Made updates relative to Substudy B. | Addition of Substudy B in protocol amendment 3. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.2.2 Vital Signs | Made updates relative to Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 8.2.3.2 Local Reactions | Added a requirement for local reactions to be assessed from the right-arm injection site. | Substudy B contains some groups in which 2 vaccinations are administered at the same visit – stipulating the right arm allows for assessment of local reactions from the deltoid muscle in which bIRV is administered. |
| 8.2.4 Clinical Safety Laboratory Assessments | Moved text from Section 10.9.8.1 to this section. | Text is applicable to both Substudies A and B. |
| 8.2.6 ECGs and Echocardiograms | Moved text from Section 10.9.8.5 to this section. Updated wording defining an ECG abnormality consistent with probable or possible myocarditis or pericarditis, for clarity. | Text is applicable to both Substudies A and B. |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Added the time period for AE/SAE collection in Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 9.2 Analysis Sets | Updated the analysis population definitions to accommodate the addition of Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 9.5 Sample Size Determination | Updated the sample size calculation to accommodate the addition of Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 10.1.5.1 Data Monitoring Committee | Added IRC responsibilities relating to Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 10.2 Appendix 2: Clinical Laboratory Tests | Added troponin I measurements associated with Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 10.6 Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments | Template text inserted regarding not assessing LFTs in Substudy B. | Addition of Substudy B in protocol amendment 3. |
| 10.9 Appendix 9: Substudy A (Phase 1) | Updated terminology throughout to change Phase 1 to Substudy A. | Addition of Substudy B in protocol amendment 3. |
| 10.9.3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS (SUBSTUDY A) and 10.9.9.3.4 Tertiary/Exploratory Endpoint(s) | CCI [redacted] | Omitted in error from protocol amendment 2. |
| 10.9.4.1 Overall Design | Removed expanded enrollment from Substudy A. | Based upon preliminary immunogenicity data, the sponsor decided not to expand enrollment into Substudy A. |
| 10.10 Appendix 10: Substudy B (Phase 1/2) | Added Substudy B. | Based upon preliminary immunogenicity data, exploration of alternative vaccination schedules including IRV as warranted. |

## Amendment 2 (04 December 2021)

### Overall Rationale for the Amendment:

Addition of an mIRV dose at approximately 8 weeks for participants having received QIV at Visit 1 and blood sample collection 28 days after 8-week mIRV/QIV dosing (Vaccination 2) to describe:

- The immune response elicited by licensed QIV following prior receipt of a modRNA vaccine, to assess potential priming of the immune response, and
- The immune response elicited by mIRV A or B following prior receipt of licensed QIV, to assess if the immune response following QIV may be enhanced.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Addition of Vaccination 2 to reflect design changes per protocol amendment 2. | To summarize design changes per protocol amendment 2. |
| 2.1 Study Rationale | Provided rationale for addition of Vaccination 2 and blood draw following QIV dosing at Visit 5. | To provide a scientific rationale for protocol amendment 2. |
| 2.2.3 Nucleoside-Modified mRNA Vaccines | Update to the number of doses of BNT162b2 administered worldwide and postmarketing safety data. | Updated data available at the time of the protocol amendment. |
| 2.3.1 Risk Assessment, and 10.9.2.3 Benefit/Risk Assessment | Addition of risk relating to vaccination of participants with mIRV within approximately 8 weeks after QIV. | Unknown safety profile of the vaccine combination. |
| 4.1 and 10.9.4.1 Overall Design | Addition of an mIRV dose at 8 weeks for participants having received QIV at Visit 1 and blood sample collection 28 days after 8-week qIRV/QIV dosing (Vaccination 2). | To describe: (1) the immune response elicited by licensed QIV following prior receipt of a modRNA vaccine, to assess potential priming of the immune response, and (2) the immune response elicited by mIRV A or B following prior receipt of licensed QIV, to assess if the immune response following QIV may be enhanced. |
| 8.2.1 Physical Examinations | Clarification that physical examinations may only be performed at Visit 1 if clinically indicated. | Physical examination is conducted at screening, hence, not mandated at Visit 1. |
| 8.2.2 Vital Signs | Detailing measurement of body temperature prior to Vaccination 2. | To confirm that no febrile illness is present. |
| 8.2.3 Electronic Diary | Detailing collection of local reactions and systemic events following Vaccination 2 via an e-diary. | Required for collection of safety data to support the primary safety objective. |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Update to the AE collection period to incorporate Vaccination 2. | Required for collection of safety data to support the primary safety objective. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.2 Analysis Sets | Addition of analysis sets following addition of Vaccination 2. | Required to support analyses related to Vaccination 2. |
| 10.1.5.1 Data Monitoring Committee | Clarification added that the IRC will be responsible for reviewing safety data only following Vaccination 1. | To ensure clarity regarding the IRC's role following addition of Vaccination 2. |
| 10.5 Appendix 5: ECG Findings of Potential Clinical Concern | Addition of mandatory protocol template text previously incorporated via administrative letter. | Mandatory protocol template text. |
| 10.6 Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments | Removal of the second paragraph stating that LFTs are not collected in this study. | Paragraph retained in error during development of protocol amendment 1, and previously removed via administrative change letter. |
| 10.9.1 SoA – Phase 1, and 10.9.8.8 Phase 1 Procedures | Addition of Visits 5A and 5B to incorporate Vaccination 2 and the 4-week post–Vaccination 2 follow-up visit. Additional procedures added to Visit 5 per the revised study design. | To accommodate the revised study design and additional study objective relating to protocol amendment 2. |
| 10.9.3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS, 10.9.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis, 10.9.9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis, and 10.9.9.3.4 Tertiary/Exploratory Endpoint(s) | Addition of a new exploratory objective relating to Vaccination 2 per the rationale for protocol amendment 2. Existing estimands revised to accommodate the revised study design. | Analysis of data collected through additional procedures implemented as part of protocol amendment 2. |
| 10.9.6.1.1 Administration | Addition of administration details for Vaccination 2. | Required following addition of Vaccination 2. |
| 10.9.6.2.1 Allocation to Study Intervention | Detail added regarding allocation of mIRV at Visits 5 and 5A. | To confirm that study intervention allocation will be conducted in an open-label manner without the use of an IRT. |
| 10.9.6.2.2 Blinding of Site Personnel | Clarifications added regarding unblinding of participants at Visit 5, and blinding of mIRV. | Updates required with addition of Vaccination 2. |
| 10.9.8 STUDY ASSESSMENTS AND PROCEDURES | Update to the total volume of blood drawn given the addition of blood draws at new visits – Visits 5A and 5B. | To reflect the addition of further blood draws in the revised study design. |
| 10.9.8.5 ECGs | Clarification added stipulating that ECGs will be read by a central vendor. | Update previously incorporated via administrative letter. |
| 10.9.8.6 Stopping Rules | Updated to confirm these rules only apply following Vaccination 1. | Not applicable following Vaccination 2. |

## Amendment 1 (14 August 2021)

## Overall Rationale for the Amendment:

Provide descriptive assessment of qIRV immunogenicity compared to licensed QIV at the earliest time point possible.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Protocol Rationale and throughout | Age of study population changed to 65 to 85 years of age | Age range focuses on target vaccine population. |
| 1.1 Protocol Rationale and throughout | Removal of Phases 2 and 3 | Following regulatory feedback. |
| 1.1 Protocol Objectives, Endpoints, and Estimands and throughout | Objectives, estimands, and endpoints updated | Edits reflect the use of a licensed QIV as active comparator, the updated age of the study population, and the removal of Phases 2 and 3. |
| 1.1 Number of Participants | Total number of participants reduced. Number of participants increased in Phase 1 | Number of participants reflects the updated study design. |
| 1.1 Data Monitoring Committee or Other Oversight Committee, and throughout | Reference to DMC was removed | Since no part of the study is blinded to the sponsor, and objectives are descriptive, an IRC can provide appropriate oversight without the need for a DMC. |
| 1.1 Statistical Methods | Text updated to detail the analysis that will be performed | Text updated to reflect the updated study design. |
| 1.2 Schema | Schema updated to reflect design changes. | Updates required to reflect the updated study design. |
| 2.3.1 Risk Assessment | Addition of risk related to anaphylaxis, myocarditis, and pericarditis | Data as reported after authorization in recipients of the COVID-19 vaccine BNT162b2, which is also based on modRNA. |
| Section 4.1. Overall Design | Text added to clarify which strains might be used in the event that the study continues beyond 2021-2022 in the northern hemisphere. | Clarification allows additional operational flexibility. |
| Section 4.2.1 Diversity of Study Population | Text updated | Text updated to reflect latest sponsor standard wording. |
| 5.1 Inclusion Criteria and 5.2 Exclusion Criteria | Criteria removed for Phase 3<br>Criteria updated for Phase 1<br>Included exclusion criterion for Phase 1 | Criteria updated to reflect change in age of study population.<br>Following regulatory feedback. |
| 6.8.1 Prohibited During the Study | Addition of prohibited modRNA-platform SARS-CoV-2 vaccine within 60 days before and 60 days after vaccination | Following regulatory feedback. |
| 8.2 Safety Assessments | Addition of clinical safety laboratories and stopping rules for ECGs, echocardiogram, and a 6-month visit for Phase 1 | Following regulatory feedback. |
| 8.3.8 Adverse Events of Special Interest | AESIs added; confirmed diagnosis of myocarditis or pericarditis | In light of cases reported after authorization in recipients of the COVID-19 vaccine BNT162b2, which is also based on modRNA. |
| 9 STATISTICAL CONSIDERATIONS | Edits made throughout this section | Edits made to reflect updated study population and study design. |
| 10.9 Appendix 9: Phase 1 | Text updated throughout section as appropriate to remove Phases 2, and reflect revised design of Phase 1 | Edits made to reflect updated study population, study design, study objectives, and monitoring for additional AESIs. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.9.8.8.11 Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis | Text added to reflect additional monitoring that will be performed | In light of cases reported after authorization in recipients of the COVID-19 vaccine BNT162b2, which is also based on modRNA. |
| Section 10.9.8.1 Clinical Safety Laboratory Assessments | Addition of clinical safety laboratories and stopping rules, addition of ECGs, echocardiogram for Phase 1 Updates made to visits | Following regulatory feedback. |
| Section 10.9.8.8.1 Screening (0 to 28 Days Before Visit 1) | Addition of screening visit for Phase 1 participants | Following regulatory feedback. |
| Section 10.9.8.8.3 Visit 2 – Day 3 Follow-up Visit (After Vaccination) – 2 to 4 Days After Visit 1 | Additional visit at Day 3 for Phase 1 participants for safety monitoring | Following regulatory feedback. |
| Section 10.10 Appendix 9 Phase 3 | Section removed. Phase 3 no longer taking place at this time | Following regulatory feedback. |
| Section 10.2 Appendix 2: Clinical Laboratory Tests | Addition of clinical laboratory tests to be done for Phase 1 participants | Following regulatory feedback. |
| Throughout, as needed | Minor editorial edits | Minor edits made to correct any typographical or administrative errors. |

## 10.14. Appendix 14: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

| Abbreviation | Term |
|---|---|
| Abs | absolute |
| ADE | adverse device effect |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AV | atrioventricular |
| β-hCG | beta-human chorionic gonadotropin |
| BCR | breakpoint cluster region |
| bIRV | bivalent influenza modRNA vaccine |
| BLQ | below the limit of quantitation |
| BNT162b2 | Pfizer's COVID-19 vaccine |
| BUN | blood urea nitrogen |
| CBER | Center for Biologics Evaluation and Research |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CRO | contract research organization |
| CSR | clinical study report |
| DILI | drug-induced liver injury |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| EC | ethics committee |
| ECC | emergency contact card |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| e-diary | electronic diary |
| EDP | exposure during pregnancy |
| EMA | European Medicines Agency |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |

| Abbreviation | Term |
|---|---|
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GMFR | geometric mean fold rise |
| GMR | geometric mean ratio |
| GMT | geometric mean titer |
| HA | hemagglutinin |
| HAI | hemagglutination inhibition assay |
| HBe | hepatitis B e |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICD | informed consent document |
| ICH | International Council for Harmonisation |
| ID | identification |
| IMP | investigational medicinal product |
| IND | investigational new drug |
| INR | international normalized ratio |
| IP manual | investigational product manual |
| IPAL | Investigational Product Accountability Log |
| IRB | institutional review board |
| IRC | internal review committee |
| IRT | interactive response technology |
| IRV | influenza modRNA vaccine |
| IV | intravenous(ly) |
| IWR | interactive Web-based response |
| LAIV | live attenuated influenza vaccine |
| LFT | liver function test |
| LLOQ | lower limit of quantitation |
| LNP | lipid nanoparticle |
| MCH | mean corpuscular hemoglobin |
| MCV | mean corpuscular volume |
| MCHC | mean corpuscular hemoglobin concentration |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mIRV | monovalent influenza modRNA vaccine |
| mITT | modified intent-to-treat |
| modRNA | nucleoside-modified messenger ribonucleic acid |

| Abbreviation | Term |
|---|---|
| MN | microneutralization |
| mRNA | messenger ribonucleic acid |
| NA | neuraminidase |
| N/A | not applicable |
| NIMP | noninvestigational medicinal product |
| PBMC | peripheral blood mononuclear cell |
| PFS | prefilled syringe(s) |
| PI | principal investigator |
| PT | prothrombin time |
| PVC | premature ventricular contraction |
| qIRV | quadrivalent influenza modRNA vaccine |
| QIV | quadrivalent influenza vaccine |
| QTcF | QT interval corrected by the Fridericia formula |
| QTL | quality tolerance limit |
| RBC | red blood cell |
| RCDC | reverse cumulative distribution curve |
| RNA | ribonucleic acid |
| RT-PCR | reverse transcription–polymerase chain reaction |
| SAE | serious adverse event |
| SADE | serious adverse device effect |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | suspected unexpected serious adverse reaction |
| TBili | total bilirubin |
| TCR | T-cell receptor |
| TOC | table of contents |
| ULN | upper limit of normal |
| US | United States |
| USADE | unanticipated serious adverse device effect |
| WBC | white blood cell |
| WOCBP | woman/women of childbearing potential |

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# Document Approval Record

| | |
|---|---|
| **Document Name:** | C4781001 Clinical Protocol Amendment 5 Clean Copy, 03-Jul-2022 |
| **Document Title:** | A PHASE 1/2 RANDOMIZED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MODIFIED RNA VA CCINE AGAINST INFLUENZA IN HEALTHY INDIVIDUALS |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| PPD | 04-Jul-2022 00 09 57 | Final Approval |
| PPD | 04-Jul-2022 13 59 43 | Business Line Approver |