Protocol C4781004

A PHASE 3, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MODIFIED RNA VACCINE AGAINST INFLUENZA COMPARED TO LICENSED INACTIVATED INFLUENZA VACCINE IN HEALTHY ADULTS 18 YEARS OF AGE OR OLDER

Statistical Analysis Plan
(SAP)

Version: 3

Date: 03 Jul 2023

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 27 Oct 2022	Amendment 1 28 Jul 2022	N/A	N/A
2 05 Apr 2023	Amendment 3 26 Mar 2023	Protocol amendment	All changes align with protocol amendment 3 except for the addition of exploratory CCI [redacted] analyses.
3 03 Jul 2023	Amendment 4 27 Jun 2023	Protocol amendment	• Updated sections associated with combining e-diary and reactogenicity events collected from the AE CRF. • Moved immunogenicity to secondary objectives (from exploratory) with 2 separate objectives to evaluate noninferiority of immune response elicited by qIRV compared to QIV using HAIs CCI [redacted] CCI [redacted] • All changes align with protocol amendment 4.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4781004.

2.1. Modifications to the Analysis Plan Described in the Protocol

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

2.2. Study Objectives, Endpoints, and Estimands

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

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.

Objectives	Estimands	Endpoints
Primary Efficacy:	**Primary Efficacy:**	**Primary Efficacy:**
Participants ≥65 Years of Age		
To demonstrate that the efficacy of qIRV is noninferior to that of QIV against LCI associated with per-protocol ILI, in participants ≥65 years of age	In participants ≥65 years of age complying with the key protocol criteria (evaluable participants) at least 14 days after study intervention: • RVE, defined as the relative reduction of the proportion of participants reporting LCI cases with associated per-protocol ILI in the qIRV group compared to the QIV group	First-episode LCI cases with associated per-protocol ILI, caused by any strain
To demonstrate that the efficacy of qIRV is superior to that of QIV against LCI associated with per-protocol ILI, in participants ≥65 years of age	In participants ≥65 years of age complying with the key protocol criteria (evaluable participants) at least 14 days after study intervention: • RVE, defined as the relative reduction of the proportion of participants reporting LCI cases with associated per-protocol ILI in the qIRV group compared to the QIV group	First-episode LCI cases with associated per-protocol ILI, caused by any strain
Participants 18 Through 64 Years of Age		
To demonstrate that the efficacy of qIRV is noninferior to that of QIV against LCI associated with per-protocol ILI, in participants 18 through 64 years of age	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants) at least 14 days after study intervention: • RVE, defined as the relative reduction of the proportion of participants reporting LCI cases with associated per-protocol ILI in the qIRV group compared to the QIV group	First-episode LCI cases with associated per-protocol ILI, caused by any strain
To demonstrate that the efficacy of qIRV is superior to that of QIV against LCI associated with per-protocol ILI, in participants 18 through 64 years of age	In participants 18 through 64 years of age complying with the key protocol criteria (evaluable participants) at least 14 days after study intervention: • RVE, defined as the relative reduction of the proportion of participants reporting LCI cases with associated per-protocol ILI in the qIRV group compared to the QIV group	First-episode LCI cases with associated per-protocol ILI, caused by any strain

Objectives	Estimands	Endpoints
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To define the safety and tolerability profile of qIRV in participants 18 through 64 years of age and ≥65 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, receiving study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination In participants 18 through 64 years of age and ≥65 years of age, separately and combined, receiving study intervention, the percentage of participants reporting: • AEs through 4 weeks after vaccination • SAEs through 6 months after vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy:	**Secondary Efficacy:**	**Secondary Efficacy:**
To evaluate the efficacy of qIRV compared to QIV against LCI or CCI associated with different definitions of ILI in participants 18 through 64 years of age and ≥65 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of study intervention: • RVE, defined as the relative reduction of the proportion of participants reporting LCI cases with associated per-protocol ILI in the qIRV group compared to the QIV group • RVE, defined as the relative reduction of the proportion of participants reporting CCI cases with associated per-protocol ILI in the qIRV group compared to the QIV group	• First-episode LCI cases with associated per-protocol ILI, caused by all matched strains • First-episode LCI cases with associated per-protocol ILI, caused by each matched strain • First-episode LCI cases with associated per-protocol ILI, caused by all unmatched strains • First-episode CCI cases with associated per-protocol ILI, caused by any strain

Objectives	Estimands	Endpoints
	• RVE, defined as the relative reduction of the proportion of participants reporting LCI associated with ILI, as defined by applying a modified CDC definition, in the qIRV group compared to the QIV group	• First-episode LCI associated with ILI, as defined by applying a modified CDC definition, caused by any strain
	• RVE, defined as the relative reduction of the proportion of participants reporting LCI cases associated with ILI, as defined by applying the WHO definition, in the qIRV group compared to the QIV group	• First-episode LCI cases associated with ILI, as defined by applying the WHO definition, caused by any strain
	• RVE, defined as the relative reduction of the proportion of participants reporting cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI in the qIRV group compared to the QIV group	• First-episode cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI
Secondary Immunogenicity:	**Secondary Immunogenicity:**	**Secondary Immunogenicity:**
To evaluate the noninferiority of immune response elicited by qIRV compared to QIV, in participants 18 through 64 years of age and ≥65 years of age (using HAI assays CCI)	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants), comparisons will be made using HAI assays CCI CCI for the influenza strains that are present in the study vaccines: • GMR of HAI titers for each strain in qIRV recipients compared to QIV recipients 4 weeks after vaccination • The difference in percentage of participants achieving seroconversion for each strain at 4 weeks after vaccination in qIRV recipients compared to QIV recipients	• HAI titers for the 2022-2023 northern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines

Objectives	Estimands	Endpoints
To evaluate the noninferiority of immune response elicited by qIRV compared to QIV, in participants 18 through 64 years of age and ≥65 years of age (using HAI assays CCI)	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants), comparisons will be made using HAI assays CCI CCI for the influenza strains that are present in the study vaccines: • GMR of HAI titers for each strain in qIRV recipients compared to QIV recipients 4 weeks after vaccination • The difference in percentage of participants achieving seroconversion for each strain at 4 weeks after vaccination in qIRV recipients compared to QIV recipients	HAI titers for the 2022-2023 northern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines
To describe the immune response elicited by qIRV, in participants 18 through 64 years of age and ≥65 years of age	In participants 18 through 64 years of age and ≥65 years of age, separately, complying with the key protocol criteria (evaluable participants), comparisons will be made using HAI assays CCI : • HAI GMTs at baseline and 4 weeks after vaccination • HAI GMFR at 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion for each strain at 4 weeks after vaccination • The proportion of participants with HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination	• HAI titers for the 2022-2023 northern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines • HAI titers for the 2022-2023 northern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines • HAI titers for the 2023 southern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines • HAI titers for the 2023 southern hemisphere seasonal strains (2×A, 2×B) recommended by WHO for CCI influenza vaccines

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

Objectives	Estimands	Endpoints
CCI		

Objectives	Estimands	Endpoints
CCI [redacted]		

Please see Table 2 for the definitions of LCI, CCI, and ILI.

Table 2. Definitions of LCI, CCI, and ILI

Acronym	Definition
Per-protocol ILI	Occurrence (new onset or worsening of preexisting condition) of at least 1 of the following respiratory symptoms concurrently with at least 1 of the following systemic symptoms: Respiratory symptoms (ongoing for at least 12 hours, or multiple episodes within a 24-hour period): • CCI [redacted] Systemic symptoms: • CCI [redacted]
ILI (modified CDC definition)	Occurrence (new onset or worsening of preexisting condition) of at least 1 of the following respiratory symptoms (ongoing for at least 12 hours, or multiple episodes within a 24-hour period) concurrently with an oral temperature of >37.2°C (>99.0°F): • Sore throat or • Cough
ILI (WHO definition)	Occurrence (new onset or worsening of preexisting condition) of a cough (ongoing for at least 12 hours, or multiple episodes within a 24-hour period) concurrently with an oral temperature of ≥38.0°C (≥100.4°F)
LCI	Influenza infection confirmed through RT-PCR or culture at the central laboratory, unless otherwise specified

Table 2. Definitions of LCI, CCI, and ILI

Acronym	Definition
CCI	Influenza infection confirmed through culture at the central laboratory,[a] unless otherwise specified
Severe LCI	Influenza infection confirmed through RT-PCR or culture at the central laboratory with associated per-protocol ILI resulting in hospitalization

a. An HAI, conducted at a central laboratory, will be used for antigenic characterization of influenza viruses recovered in cultured samples to determine if they are matched strains to the vaccine.

2.2.1. Primary Estimand(s)

The primary estimands for the primary noninferiority and superiority efficacy objectives for each age group (18 through 64 years of age, ≥65 years of age) will use the hypothetical strategy and estimate the RVE when an intercurrent event does not occur. In other words, the RVE is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed. The efficacy estimands for the primary efficacy objectives for each age group will be defined similarly.

- The efficacy estimands will have the following 5 attributes:
  - **Population:** Participants who receive 1 dose of study intervention, as defined by the inclusion and exclusion criteria.
  - **Variables:** First-episode LCI cases with associated per-protocol ILI, caused by any strain at least 14 days following vaccination.
  - **Treatment condition:** qIRV, or seasonal QIV, administered on Day 1.
  - **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the RVE:
    - Not receiving the vaccine as randomized.
    - Not meeting the study inclusion/exclusion criteria.
    - Having important protocol deviations (including but not limited to, having received a prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).

    All data after intercurrent events, if collected, will be excluded.
  - **Population-level summary:** RVE as estimated by 1 – risk ratio of the variable (first-episode LCI cases) in the qIRV group compared to the QIV group.

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

- The reactogenicity estimand (local reactions and systemic events) has the following 5 attributes:
    - **Population:** Participants 18 years of age or older who receive 1 dose of study intervention.
    - **Variables:** Each prompted item from the e-diary from Days 1 through 7 following vaccinations and coded reactogenicity AEs (as determined by the study clinician) from Days 1 through 7.
    - **Treatment condition:** qIRV, or seasonal QIV, administered on Day 1.
    - **Intercurrent events:** All data after an intercurrent event (receiving a prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, missing e-diary entries on certain days, discontinuation of the study, etc), if collected, will be included.
    - **Population-level summary:** The rates of reporting each prompted reactogenicity item and/or coded reactogenicity AE will be estimated, by study intervention (qIRV or seasonal QIV), for each age group (18 through 64 years of age, ≥65 years of age).
- The AE and SAE estimands have the following 5 attributes:
    - **Population:** Participants 18 years of age or older who receive 1 dose of study intervention.
    - **Variables:**
        - AEs reported through 4 weeks after vaccination.
        - SAEs reported through 6 months after vaccination.
    - **Treatment condition:** qIRV, or seasonal QIV, administered on Day 1.
    - **Intercurrent events:** All data after an intercurrent event (receiving a prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, discontinuation of the study, etc), if collected, will be included.
    - **Population-level summary:** The rates of reporting AEs and SAEs will be estimated, by study intervention (qIRV or seasonal QIV), for each age group (18 through 64 years of age, ≥65 years of age) and overall (≥18 years of age).

2.2.2. Secondary Estimand(s)

2.2.2.1. Immunogenicity

The estimands for the secondary immunogenicity objectives for each age group (18 through 64 years of age and ≥65 years of age) will use the hypothetical strategy. The estimands for the secondary immunogenicity objectives for each assay type (CCI [redacted]) and age group will be defined similarly.

- The secondary immunogenicity estimands will have the following 5 attributes for each assay type and age group:
  - **Population:** Participants within each age group who receive 1 dose of study intervention, as defined by the inclusion and exclusion criteria.
  - **Variables:**
    - HAI titers for each strain at baseline and 4 weeks after vaccination.
    - Presence of HAI seroconversion for each strain at 4 weeks after vaccination.
    - HAI titer fold rise for each strain from before vaccination to 4 weeks after vaccination.
    - Presence of HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination.
    - Above summary will be produced separately for HAI titers derived from HAI assays CCI [redacted]
  - **Treatment condition:** qIRV, or seasonal QIV, administered on Day 1.
  - **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:
    - Not receiving the vaccine as randomized.
    - Not meeting the study inclusion/exclusion criteria.
    - Having important protocol deviations (including received a prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).
    - Blood was taken outside of the defined window of CCI [redacted] after vaccination.

    All data after intercurrent events, if collected, will be excluded.

- **Population-level summary:**

  - GMR of HAI titers for qIRV to HAI titers for QIV at 4 weeks after vaccination and the difference between qIRV and QIV in the proportion of participants achieving HAI seroconversion at 4 weeks after vaccination will be estimated for each strain.

  - HAI GMTs at each time point and GMFRs from before vaccination to 4 weeks after vaccination, the proportion of participants achieving HAI seroconversion at 4 weeks after vaccination, and the proportion of participants with HAI titers ≥1:40 before vaccination and at 4 weeks after vaccination, will be estimated, by vaccine group, for each strain.

  - The above summary will be produced separately for HAI titers derived from HAI assays CCI [redacted]

2.2.2.2. Efficacy

The estimands for the secondary efficacy objective are defined in a similar way as the primary efficacy estimands, except with different variables and/or population-level summaries listed in the table below.

Secondary Efficacy Objective	Population	Variable	Population-Level Summary
To evaluate the efficacy of qIRV compared to QIV against LCI or CCI associated with different definitions of ILI in participants 18 through 64 years of age and ≥65 years of age	Participants 18 through 64 years of age and ≥65 years of age who receive 1 dose of study intervention, as defined by the inclusion and exclusion criteria	First-episode LCI cases with associated per-protocol ILI, caused by all matched strains, at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)
		First-episode LCI cases with associated per-protocol ILI, caused by each matched strain, at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)
		First-episode LCI cases with associated per-protocol ILI, caused by all unmatched strains, at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)

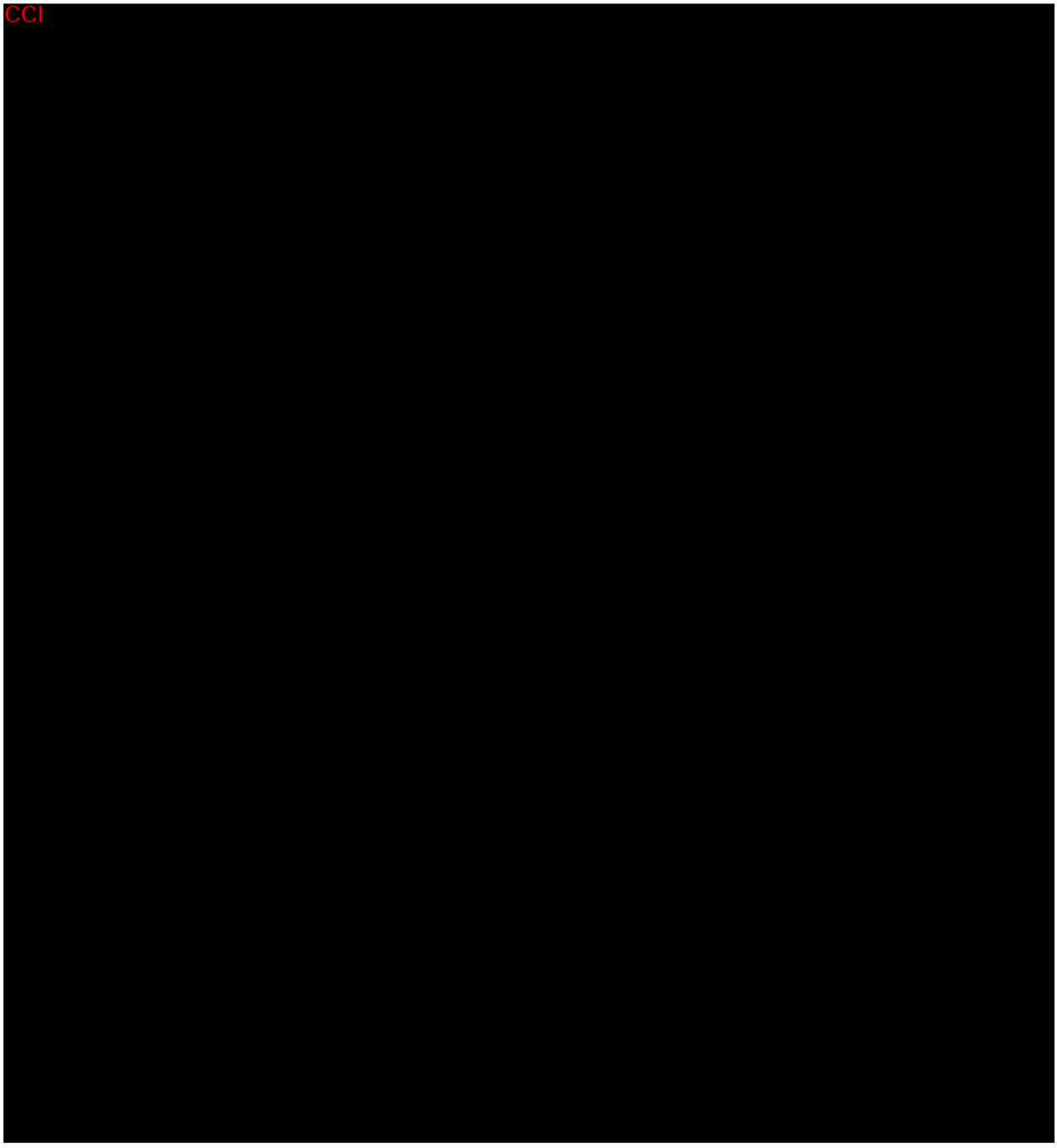
Secondary Efficacy Objective	Population	Variable	Population-Level Summary
		First-episode CCI cases with associated per-protocol ILI, caused by any strain, at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)
		First-episode LCI cases associated with ILI, as defined by applying a modified CDC definition, caused by any strain, at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)
		First-episode LCI cases associated with ILI, as defined by applying the WHO definition, caused by any strain at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)
		First-episode cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI, caused by any strain, at least 14 days following vaccinations	RVE estimated for each age group (18 through 64 years of age, ≥65 years of age)

2.2.3. Additional Estimand(s)

CCI

[redacted]

CCI



CCI

- CCI

2.3. Study Design

This is a Phase 3, randomized, observer-blinded study to evaluate the efficacy, safety, tolerability, and immunogenicity of qIRV-encoding HA of 4 seasonally recommended strains (2 A strains and 2 B strains) in healthy individuals ≥18 years of age.

Up to approximately 36,200 participants will be enrolled in this study and stratified by age as follows:

- Up to approximately CCI participants ≥65 years of age will be enrolled and randomized CC to receive 1 dose of either qIRV or seasonal QIV comparator.
- Up to approximately CCI participants 18 through 64 years of age will be enrolled and randomized CC to receive 1 dose of either qIRV or seasonal QIV comparator. Enrollment of participants 18 through 64 years of age is contingent on obtaining satisfactory Phase 1/2 data in participants of this age and will only proceed if regulatory authority endorsement is obtained to do so. Enrollment into each of the 2 age strata (18 through 64 years of age and ≥65 years of age) may therefore occur independently. The qIRV dose level per strain to be used will be based on Phase 2 safety and immunogenicity data and will be detailed in the IPM; the qIRV dose level may differ by age stratum.
- In each age stratum:
  - Approximately CCI participants will be included in a reactogenicity subset. For participants in the reactogenicity subset, a reactogenicity e-diary will be completed by each participant for 7 days following vaccination.
  - Approximately CCI participants will be included in an immunogenicity subset. Blood samples of approximately 15 mL will be collected for immunogenicity assessments prior to vaccination and at 4 weeks and 6 months after vaccination. An additional optional blood sample of 50 mL may be collected from participants who consent to the time points for assessment of CCI ; the number of participants asked to provide these samples will be determined by Pfizer, contingent on operational considerations. Approximately CCI participants ≥18 years of age will be asked to consent to alternatively providing 50-mL, rather than 15-mL, blood samples at the same time points, which will be used for immunogenicity assessments as well as assay development.
  - Participants may be enrolled in either or both of the subsets described above.

Efficacy will be assessed in this study through surveillance for ILI. Following vaccination, all participants will be prompted approximately weekly to complete a questionnaire, using an e-diary or equivalent technology, designed to identify ILI. This questionnaire will also be completed any time the participant develops symptoms of ILI. If a participant develops ILI, 2 midturbinate swabs will be collected (1 from each nostril), either by the participant or by site staff at an ILI visit. These swabs will then undergo RT-PCR and culture testing at a

central laboratory to confirm the presence of influenza virus. Culture testing will only be conducted on swab samples from participants with an RT-PCR–positive swab sample from the corresponding ILI visit. Surveillance for ILI will continue until each influenza season ends (as judged by Pfizer based on epidemiological data).

If enrollment is insufficient, or it is projected that insufficient first-episode LCI cases associated with per-protocol ILI, caused by any strain, will accrue during the northern hemisphere 2022-2023 influenza season (as judged by Pfizer), this study may be extended into a second influenza season within the southern hemisphere.

CCI [redacted] Of these additional participants:

- The number of participants 18 through 64 years of age or ≥65 years of age will be determined by Pfizer based on enrollment in each of these age strata during the northern hemisphere 2022-2023 influenza season and/or projected LCI case accrual in each age stratum.

- Up to approximately CCI participants in each age stratum will be included in a reactogenicity subset. For participants in the reactogenicity subset, a reactogenicity e-diary will be completed by each participant for 7 days following vaccination.

- Up to approximately CCI participants in each age stratum will be included in an immunogenicity subset. Blood samples of approximately 15 mL will be collected for immunogenicity assessments prior to vaccination and 4 weeks and 6 months after vaccination.

The primary efficacy analysis may be conducted in each age stratum when at least CCI first-episode evaluable LCI cases associated with per-protocol ILI, caused by any strain, have been accrued in a given age stratum. Hence, the primary efficacy analysis in each age stratum may be conducted at different times and the hypothesis testing across the 2 age strata will be independent. Within each age stratum, hypothesis testing relating to the VE and immunogenicity objectives will occur in a hierarchical manner, as described in Section 5.1.3.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Efficacy Endpoint

- First-episode LCI cases with associated per-protocol ILI, caused by any strain, at least 14 days following vaccination.

3.1.1.1. LCI Case Derivation With Associated Per-Protocol ILI

To meet the requirement of LCI case definition with per-protocol ILI, an ILI (new onset or worsening of preexisting condition) should have at least 1 respiratory symptom concurrently with at least 1 systemic symptom and confirmed through RT-PCR or culture testing at the central laboratory (ie, positive result for any strain). The respiratory symptoms and systemic symptoms are listed below:

Respiratory symptoms (ongoing for at least 12 hours, or multiple episodes within a 24-hour period):

- CCI
- [redacted]

Systemic symptoms:

- CCI
- [redacted]

The 2 midturbinate swabs will be collected for testing at a central laboratory using RT-PCR and viral culture testing to detect influenza viruses in the respiratory specimen. Culture testing will only be conducted on swab samples from participants with an RT-PCR–positive swab sample from the corresponding ILI visit. The ILI visit (site, telehealth, home health) and swab samples should be done from the concurrent respiratory and systemic symptom start date and up to 5 days after the participant no longer meets the per-protocol ILI

definition. The symptoms presented and initial symptom onset date are recorded at an ILI visit.

3.1.1.2. First-Episode LCI Case Derivation With Associated Per-Protocol ILI

For the primary efficacy endpoint, only first-episode LCI cases with per-protocol ILI, with initial symptom onset date between Day 15 (ie, 14 days after vaccination) and the end of the influenza season (all inclusive), or the data cutoff date for performing primary efficacy analysis as determined by the sponsor, will be considered. Additionally, if there are any important protocol deviations before/during ILI onset, the cases from these ILIs will not be included in the evaluable efficacy population analysis.

The important protocol deviations are identified throughout the study via study monitor, medical, and other team member review. In the case in which there are multiple episodes of LCI with per-protocol ILI, only the first-episode that is between Day 15 and the end of the influenza season, or the data cutoff date for performing primary efficacy analysis as determined by the sponsor, will be included as the primary endpoint.

Following the ILI visit being initiated, if new OR recurrent symptoms that meet per-protocol requirements for an ILI visit emerge, there is no minimum time between symptom start and/or resolution that would preclude an additional ILI visit. Investigators should discuss the symptoms with the participant and use their clinical judgment to determine if such new OR recurrent symptoms are part of a single ILI or a second ILI, and therefore if an additional ILI visit is required.

3.1.2. Primary Safety Endpoint

- Local reactions for up to 7 days following vaccination.
- Systemic events for up to 7 days following vaccination.
- AEs through 4 weeks after vaccination.
- SAEs through 6 months after vaccination.

It has been requested by the regulatory agency to combine reactogenicity data from different sources, such as the e-diary and AE CRF. Since the AE CRF does not designate a specific page to collect reactogenicity data that are missing from the e-diary, Pfizer has adopted a process of providing a listing of AEs reported within 7 days after vaccination to the clinical team to review/query the AEs and flag the preferred terms that should be considered as reactogenicity events before the database is locked. AEs reported on the same day of vaccination, but missing AE start times are defaulted to AEs after vaccination. Only those AEs reported within 7 days with completed AE start dates after vaccination, matched with the flagged preferred terms, will be pooled with reactogenicity data from the e-diary. If the same reactogenicity event is reported on the same day from both the e-diary and AE CRF, the highest grade from the 2 data sources will be used for that specific day.

It should be noted that the data collection in the AE CRF is different from that in the e-diary:

- For redness, swelling, and fever, the measured size and temperature are recorded in the e-diary, but not in the AE CRF. Therefore, the maximum grading for the 3 items reported in the e-diary will be based on actual size and FDA toxicity grading scale, but the maximum grading of the 3 reactogenicity terms from the AE CRF will be based on the grading scale in the CRF page. Across the 7 days, only the maximum grading from both sources will be used for the aggregated severity analysis, though the grading algorithm is different between the 2 data sources.

- For pain at the injection site and all systemic events, the severity grading algorithm in the e-diary and AE CRF may not be the same; the highest severity grade will be used.

- Both related and nonrelated solicited reactogenicity events that are recorded on the AE CRF will be included.

- If a participant did not have any e-diary data transferred, the AE CRF data will not be used for derivation because the AE CRF is considered as "supplemental" for reactogenicity data missed on certain days but not all 7 days. In other words, if a participant did not report any e-diary data, the participant will not be included in the reactogenicity population.

Related and nonrelated reactogenic SAEs will be presented in both reactogenicity and AE tables. Immediate AEs and AEs leading to discontinuation, as well as reactogenicity AEs for participants not in the reactogenicity population, will be summarized with the AE tables.

In addition, a separate reactogenicity analysis will also be performed without combining any reactogenicity data collected from the AE CRF.

3.1.2.1. Local Reactions

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

Presence or Absence

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

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

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

For each local reaction and any local reaction on any day, Table 3. and Table 4, respectively, explain the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of vaccination.

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

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

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

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

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

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

Variables for the presence of each local reaction and presence of any local reaction will be similarly derived as in Table 3 and Table 4 when combining local reaction data from the AE CRF and e-diary data.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring CCI [redacted] and then categorized during analysis as absent, mild, moderate, or severe, based on the grading scale in Table 5 with combined local reaction data from both the e-diary and AE CRF. For the local reaction analysis, without combining local reaction data from the AE CRF, a similar grading scale as Table 5 (without AE CRF data) will be used. CCI [redacted] Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[a]
Pain at the injection site	Does not interfere with activity (from the e-diary) or mild from the AE CRF	Interferes with activity (from the e-diary) or moderate from the AE CRF	Prevents daily activity (from the e-diary) or severe from the AE CRF	Emergency room visit or hospitalization for severe pain Or life-threatening from the AE CRF
Redness	2.0 cm to 5.0 cm CCI [redacted] or mild from the AE CRF	>5.0 cm to 10.0 cm CCI [redacted] or moderate from the AE CRF	>10 cm CCI [redacted] or severe from the AE CRF	Necrosis or exfoliative dermatitis Or life-threatening from the AE CRF
Swelling	2.0 cm to 5.0 cm CCI [redacted] or mild from the AE CRF	>5.0 cm to 10.0 cm CCI [redacted] or moderate from the AE CRF	>10 cm CCI [redacted] or severe from the AE CRF	Necrosis Or life-threatening from the AE CRF

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

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

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

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

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

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

Onset Day of Each Local Reaction

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

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

3.1.2.2. Systemic Events

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

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

The variables associated with the systemic events will be computed in a way similar to the way local reactions are computed (see Section 3.1.2.1).

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

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6 with combined systemic data from both the e-diary and AE CRF. For the systemic analysis, without combining systemic data from the AE CRF, a similar grading scale as Table 6 (without AE CRF data) will be used.

Table 6. Systemic Event Grading Scale

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

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

Oral temperature will be collected in the evening, daily, for 7 days following vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary.

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

Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 7 for summary of maximum temperature. Fever will be grouped into ranges for the analysis according to Table 7 with combined fever data from both the e-diary and AE CRF. For the fever, without combining systemic data from AE CRF, a similar grading scale as Table 7 (without AE CRF data) will be used.

Table 7. Scale for Fever

Mild: ≥38.0°C to 38.4°C (100.4°F to 101.1°F) from the e-diary or mild grade from the AE CRF
Moderate: >38.4°C to 38.9°C (101.2°F to 102.0°F) from the e-diary or moderate grade from the AE CRF
Severe: >38.9°C to 40.0°C (102.1°F to 104.0°F) from the e-diary or severe grade from the AE CRF
Grade 4: >40.0°C (>104.0°F) from the e-diary or life-threatening grade from the AE CRF

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

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

3.1.2.3. Use of Antipyretic Medication

The use of antipyretic medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the day of vaccination. For the use of antipyretic medication from Day 1 through Day 7 after vaccination, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.2.1) where applicable.

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

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

3.1.2.4. Adverse Events

Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer vaccine data standard rules. AEs will be collected from the time the participant provides informed consent through 4 weeks following vaccination.

Any AE reported in the CRF and considered as a reactogenicity event (Section 3.1.2) during clinical review and the data pooling process will not be included in any of the derivation included in Section 3.1.2.4 and Section 3.1.2.5. However, if those reactogenicity AEs lead to discontinuation, or are immediate AEs, SAEs, or medically attended AEs, they will still be included in the AE data.

The following derivations will be included for each participant:

- Any AE reported.
- Any related AE reported.
- Any immediate AE (assess acute reactions for at least 30 minutes after study intervention administration).
- Any severe AE.
- Any life-threatening AE.
- Any AE leading to study withdrawal.
- Any AE leading to death.
- Any AESI.
    - A confirmed diagnosis of myocarditis or pericarditis.

The following analysis intervals will be defined for the above endpoints:

- From Day 1 (vaccination day) through 7 days after vaccination.
- From Day 8 through 4 weeks after vaccination (Visit 3).
- From Day 1 through 4 weeks after vaccination (Visit 3).

The analysis interval of "From 4 weeks after vaccination (Visit 3) through 6 months after vaccination (Visit 4)" will also be defined for endpoints of 'Any AE leading to death' and 'Any AESI'.

3.1.2.5. Serious Adverse Events

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

The following analysis intervals will be defined for SAEs:

- From Day 1 (vaccination day) through 7 days after vaccination.

- From Day 8 through 4 weeks after vaccination (Visit 3).
- From 4 weeks after vaccination (Visit 3) through 6 months after vaccination (Visit 4).
- From Day 1 through 4 weeks after vaccination (Visit 3).
- From Day 1 through 6 months after vaccination (Visit 4).

3.2. Secondary Endpoint(s)

3.2.1. Secondary Immunogenicity Endpoints (CCI [redacted]

- HAI titers for each strain at baseline and 4 weeks after vaccination.
- Presence of HAI seroconversion for each strain at baseline and 4 weeks after vaccination.
- HAI titer fold rise for each strain from before vaccination to 4 weeks after vaccination.
- Presence of HAI titers ≥1:40 for each strain before vaccination and at 4 weeks after vaccination.

3.2.2. Secondary Efficacy Endpoints

- First-episode LCI cases with associated per-protocol ILI, caused by any strain, in each age population.
- First-episode LCI cases with associated per-protocol ILI, caused by all matched strains.
- First-episode LCI cases with associated per-protocol ILI, caused each matched strain.
- First-episode LCI cases with associated per-protocol ILI, caused all unmatched strains.
- First-episode CCI cases with associated per-protocol ILI, caused by any strain.
- First-episode LCI cases associated with ILI, as defined by applying a modified CDC definition, caused by any strain.
- First-episode LCI cases associated with ILI, as defined by applying the WHO definition, caused by any strain.
- First-episode cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI.

A vaccine-matched (antigenically similar) strain is defined as a CCI [redacted] relative to a reference serum. This analysis is conducted as part of the AMT, conducted at a central laboratory, and will be used for antigenic characterization of influenza viruses recovered in cultured samples to determine if they are matched strains to the vaccine, as stated "matched strains" in the above efficacy endpoints. Some examples of

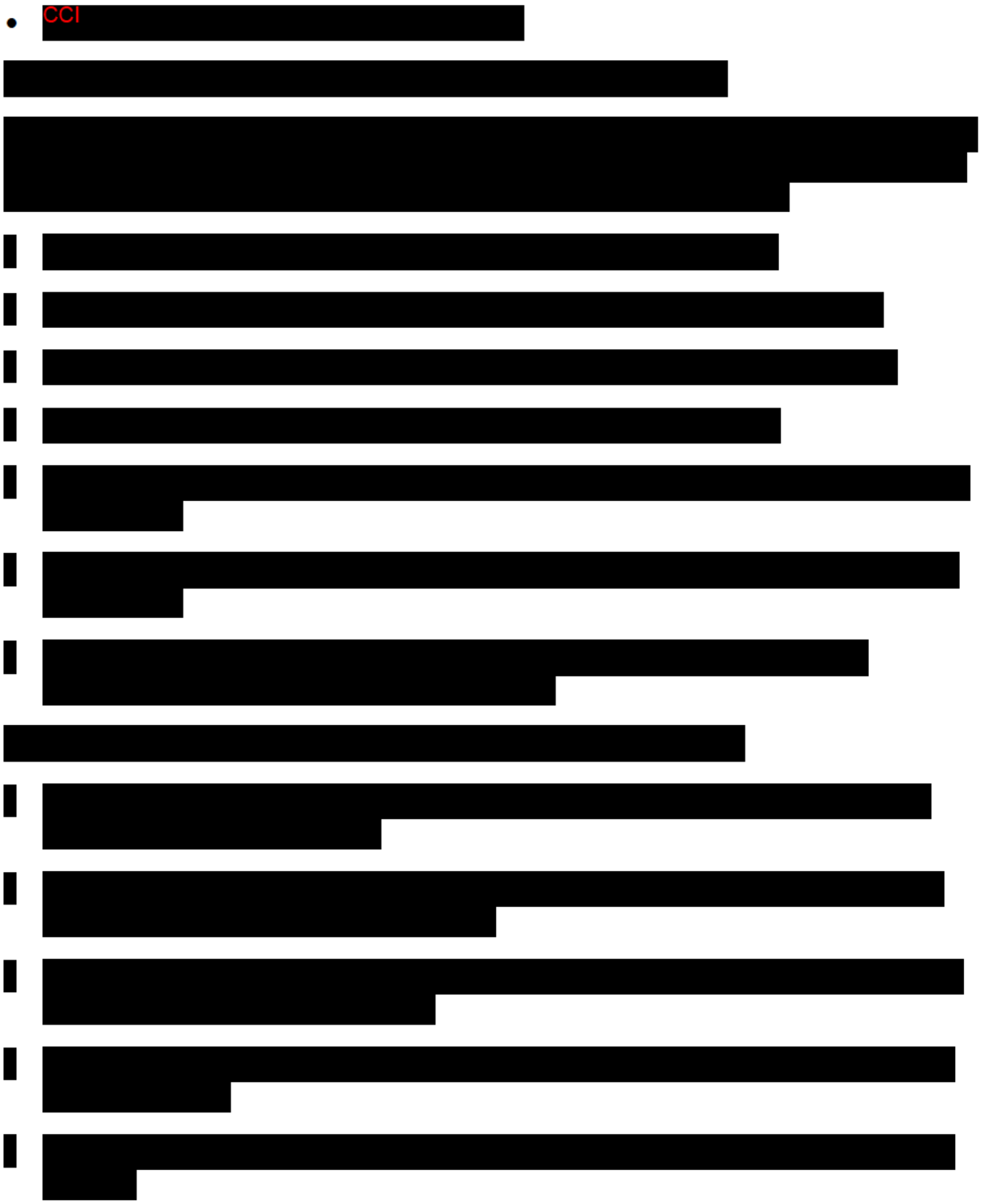
matched/unmatched strains for A/B strains, based on PCR laboratory and culture results, are in the table below.

Strain	Confirmed PP ILI PCR+	AMT A/CCI	AMT A/CCI
Matched A/CCI	POS	POS	NEG
Matched A/CCI	POS	NEG	POS
Unmatched A	POS	NEG	NEG
Strain	**Confirmed PP ILI PCR+**	**AMT B/CCI**	**AMT B/CCI**
Matched B/CCI	POS	POS	NEG
Matched A/CCI	POS	NEG	POS
Unmatched B	POS	NEG	NEG

3.3. Other/Exploratory Endpoint(s)

CCI

- CCI [redacted]



3.4. Baseline Variables

Unless otherwise specified, the last nonmissing measurements or samples collected prior to vaccination are considered the baseline data for the assessments.

3.4.1. Demographics and Medical History

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

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

Medical history will be categorized according to MedDRA.

3.4.2. E-Diary Completion

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

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

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

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

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

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

The name and date of administration for any concomitant medications and nonstudy vaccinations received from 28 days prior to study enrollment until the last visit (Visit 4) will be collected and recorded in the CRF. Details of concomitant medications and vaccination will be recorded in the CRF, and concomitant medications used to treat ILI symptoms will be collected in the ILI CRF.

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

- Prior receipt of any COVID-19 vaccine.
- Prior receipt of any pneumococcal vaccine.
- Licensed influenza vaccine, if received within the 12 months prior to enrollment.
- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 4).
- Prohibited medications listed in Section 6.9.1 of the protocol, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

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

3.5. Safety Endpoints

Local reaction, systemic event, AE, AESI, and SAE assessments have been described above in the primary safety endpoints.

3.5.1. Adverse Events

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (refer to Section 6.6.1.

- Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's safety review plan.
- Tier 2 events: These are events that are not Tier 1 but are "common." A MedDRA PT is defined as a Tier 2 event if its incidence is at CCI in any study intervention group.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.5.2. Physical Examinations, Including Vital Signs

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

The participant's oral temperature will be measured prior to vaccination. Weight and height will also be measured prior to vaccination. Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

3.5.3. Laboratory Data

Clinical safety laboratory assessments will not be collected in this study.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IWRS.
Evaluable immunogenicity (HAI assays CCI [redacted])	All participants included in the immunogenicity subset who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame (CCI [redacted]), have at least 1 valid and determinate assay result (HAI assays CCI [redacted]) at the 4-week postvaccination visit, and have no important protocol deviations.
Evaluable immunogenicity (HAI assays CCI [redacted])	All participants included in the immunogenicity subset who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame (CCI [redacted]), have at least 1 valid and determinate assay result (HAI assays CCI [redacted]) at the 4-week postvaccination visit, and have no important protocol deviations.
mITT immunogenicity (HAI assays CCI [redacted])	All randomized participants in the immunogenicity subset who receive the study intervention and have at least 1 valid and determinate assay result (HAI assays CCI [redacted]) after vaccination.
mITT immunogenicity (HAI assays CCI [redacted])	All randomized participants in the immunogenicity subset who receive the study intervention and have at least 1 valid and determinate assay result (HAI assays CCI [redacted]) after vaccination.
Evaluable efficacy	All participants who are eligible, receive the study intervention to which they were randomized, and have no important protocol deviations, with surveillance starting at least 14 days after vaccination.
mITT efficacy	All randomized participants who receive the study intervention.

Population	Description
Safety	All participants who receive the study intervention.
Reactogenicity e-diary safety	All participants who receive the study intervention and have at least 1 day of e-diary data transferred for reactogenicity.

In addition, the mITT analysis set will be defined for participants who consent for isolation of [redacted] and also for participants who may be selected for [redacted].

mITT immunogenicity ([redacted])	All randomized participants in the immunogenicity subset who receive the study intervention and have at least 1 valid and determinate [redacted] sample result after vaccination.
mITT immunogenicity [redacted]	All randomized participants in the immunogenicity subset who receive the study intervention and have at least 1 valid and determinate [redacted] result after vaccination.

Important protocol deviations will be determined by clinical review. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's study medical monitor, would materially affect the assessment of immunogenicity or efficacy, eg, participant receipt of a prohibited vaccine or medication/treatment that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those participants with protocol deviations before any analysis is carried out.

Note, participants who have confirmed cases prior to an important protocol deviation are included in the evaluable efficacy population.

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

The APE flags for this study are as follows:

- YES-POP1 (participants excluded from the safety population)
- YES-POP2 (participants excluded from the evaluable immunogenicity populations [redacted])
- YES-POP3 (participants excluded from the evaluable efficacy population)
- YES-POP4 (participants identified as multiple enrollments at different sites)

The safety analyses are based on the safety population. Participants will be summarized by study intervention group according to the study interventions they actually received.

For all the immunogenicity endpoints, the analysis will be based on the appropriate evaluable immunogenicity population. An additional analysis may be performed based on the mITT immunogenicity population if there is a large enough difference [redacted] in sample size[1] between the mITT immunogenicity population and the evaluable immunogenicity population separately for each assay type. Participants will be summarized according to the study intervention group to which they were randomized.

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

Randomized but not vaccinated: These participants will be included in the randomly assigned population and excluded from any safety analyses.

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

Participants who had important protocol deviations or discontinued from the study before Day 15 (within 2 weeks after vaccination) will be excluded from the evaluable efficacy population.

Participants who were enrolled in the wrong age cohort per their chronological age at the time of enrollment and who were dosed with the study vaccination will be excluded from the evaluable efficacy and evaluable immunogenicity populations. These participants will be included in the mITT population for immunogenicity and efficacy analyses. Safety data for these participants will be populated on listings separate from those participants enrolled in the correct cohort.

Participants who were enrolled in the wrong age cohort per their chronological age at the time of enrollment but were dosed with licensed QIV will not be excluded from the evaluable efficacy and evaluable immunogenicity populations if there are no important protocol deviations and they are meeting other criteria of the evaluable efficacy/immunogenicity population. Safety data for these participants will be included with all participants who received licensed QIV per their chronological age at the time of enrollment.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The hypotheses for the primary efficacy and secondary immunogenicity objectives are stated below.

5.1.1. Efficacy

The primary efficacy objective of the study is to evaluate the noninferiority and superiority of the VE of qIRV against first-episode LCI cases with associated per-protocol ILI (caused by any strain), with symptom onset from 14 days after vaccination, compared to QIV for each age group (participants 18 through 64 years of age and ≥65 years of age) independently.

The statistical hypothesis is defined below, and the evaluable efficacy population will be used for hypothesis testing.

H_0: RVE [redacted]

[redacted]

H_0: p [redacted]

The following hypothesis for superiority of VE of qIRV against first-episode LCI cases with associated per-protocol ILI (caused by any strain), with symptom onset from 14 days after vaccination, compared to QIV, will be tested for each age group.

H_0: RVE [redacted]

The primary noninferiority efficacy objective for each age group will be achieved if the lower bound of the 95% CI of RVE is [redacted], and the superiority efficacy objective will be met if the lower bound of the 95% CI of RVE is [redacted].

5.1.2. Immunogenicity

A secondary immunogenicity objective of the study is to evaluate the noninferiority of the immune response to qIRV at 4 weeks after vaccination compared to QIV for each age stratum (participants 18 through 64 or ≥65 years of age). For antibody titers measured by HAI assays [redacted], 2 statistical hypotheses for each targeted strain will be defined, as described below, and the evaluable immunogenicity population (HAI assays [redacted]) will be used for hypothesis testing in each age stratum:

H_{01}: CCI [redacted]

where CCI [redacted] corresponds to a CCI [redacted] margin for noninferiority, and CCI [redacted] from the qIRV group and the QIV group, respectively, measured 4 weeks after vaccination.

H_{02}: CCI [redacted]

where CCI [redacted] are the proportions of participants achieving seroconversion at 4 weeks after vaccination for the qIRV group and QIV group, respectively, measured 4 weeks after vaccination.

For antibody titers measured by HAI assays CCI [redacted] 2 statistical hypotheses for each targeted strain will be defined as described above based on the evaluable immunogenicity population (HAI assays CCI [redacted].

5.1.3. Multiplicity Adjustment

There are 2 hypothesis tests for the primary efficacy objectives (noninferiority, superiority) in each group (18 through 64 years of age, ≥65 years of age).

There are 8 hypothesis tests for the secondary immunogenicity objectives CCI [redacted] assays, separately, with 2 statistical hypotheses for each of the 4 targeted strains for each age stratum (participants 18 through 64 and ≥65 years of age).

Only immunogenicity data collected from the CCI [redacted] will be used for the immunogenicity noninferiority objectives.

For both age strata (participants 18 through 64 and ≥65 years of age), the hypothesis for the primary noninferiority efficacy objective will be tested first, followed by the hypothesis for the primary superiority efficacy objective. The superiority efficacy objective will be tested only after the noninferiority efficacy objective has been achieved. The hypotheses related to the secondary immunogenicity objective (HAI assays CCI [redacted]) for each age stratum will be tested after both primary efficacy objectives in the respective age stratum have been achieved. Within the set of hypotheses related to HAI assays CCI [redacted], the hypotheses testing will be performed in their associated strain, CCI [redacted]. The hypotheses related to the secondary immunogenicity objective assessed using HAI assays CCI [redacted] for each age stratum will be tested with same testing order CCI [redacted] (CCI [redacted]) after the secondary immunogenicity objective (HAI assays CCI [redacted]) in the respective age stratum has been achieved.

CCI [redacted]

A fixed-sequence testing procedure will be used to control the overall 1-sided type I error at CCI [redacted] for all efficacy and immunogenicity hypotheses within each age stratum. The 1-sided alpha level of CCI [redacted] will be used for each hypothesis that can be tested based on this strategy.

All vaccine efficacy estimations with any additional LCI cases collected after primary analysis will be descriptively summarized with a 95% CI. No type I error will be allocated to the remaining secondary endpoints or exploratory endpoints.

5.2. General Methods

Descriptive statistics for binary variables are the proportion (%) and the numerator (n) and the denominator (N) used in the proportion calculation. The 95% CI for percentage, and for the difference in percentages, may also be presented, where appropriate.

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

5.2.1. Analyses for Binary Endpoints and Count 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)[2] and implemented in SAS PROC FREQ.

The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen[3] method.

Descriptive statistics for count data are incidence rate, the numerator (number of events observed) and the denominator (total person-years of follow-up) used in the incidence rate calculation, and the 95% CIs where applicable.

The exact 95% CI for incidence rates for each group may be computed using the method of Ulm,[4] based on the link between the chi-square distribution and the Poisson distribution.

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

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

5.2.2.2. Geometric Mean Fold Rises

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

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's

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

5.2.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.4. Reverse Cumulative Distribution Curves

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

5.2.3. Analyses for Efficacy Endpoints

Efficacy will be calculated for laboratory-confirmed influenza, caused by any influenza viral types/subtypes, associated with the occurrence of a protocol-defined ILI.

5.2.3.1. Comparing Attack Rates

The efficacy of qIRV relative to QIV (RVE) will be estimated by: CCI [redacted] for each age group (18 through 64 years of age, ≥65 years of age), separately.

where RVE is the efficacy of qIRV relative to QIV, RR is the attack rate ratio, CCI [redacted]

CIs for the RVE will be calculated by an exact method conditional on the total number of cases in both groups.

The above RVE can also be written as:

RVE = CCI [redacted]

Given the total number of cases, C_{qIRV} has a binomial distribution[1] B CCI [redacted]. Thus, a CI for C [redacted] C may be constructed using the exact Clopper-Pearson method for binomial proportions.

5.2.3.2. Comparing Person-Time Data

The RVE can also be estimated by comparing person-time data[5] between study interventions. Two statistical methods (Poisson regression and Cox regression) are listed below.

5.2.3.2.1. Poisson Regression

The efficacy of qIRV relative to QIV (RVE) can also be estimated by:
RVE = 1 - IRR = 1 - CCI [redacted]

where RVE is the efficacy of qIRV relative to QIV; IRR is the incidence rate ratio for qIRV to QIV, CCI [redacted]

The incidence rate ratio IRR, CCI [redacted], and associated 95% CI, will be obtained using a scaled Poisson regression model. The offset will be the duration of follow-up in the influenza season for a given participant and the scale parameter will be estimated by the Pearson method, so the RVE and associated 95% CI can be estimated based on RVE = 1 - IRR.

Poisson regression with the study intervention as a covariate will be fit for each age group (18 through 64 years of age, ≥65 years of age), separately.

For participants with confirmed influenza (eg, first-episode LCI case with associated per-protocol ILI caused by any strain), their time of confirmed influenza will be used to calculate their person-time. For participants without confirmed influenza, CCI [redacted] will be used to calculate their person-time.

5.2.3.2.2. Cox Regression Model

The RVE can also be estimated by Cox regression, which utilizes the time to the first-episode of LCI cases.

$$RVE = 1 - \Theta_{qIRV}(t) / \Theta_{QIV}(t)$$
$$= 1 - \Theta$$

where:

$\Theta_{qIRV}(t)$ = hazard rate (or force of illness in infectious diseases) in the qIRV group

$\Theta_{QIV}(t)$ = hazard rate in the QIV group

which can be further defined as $\Theta(t) = f(t)/S(t)$, for which f(t) is the rate of first-occurrence confirmed influenza per unit time (t) and S(t) is the survival function, ie, function of time without influenza events.

Cox regression requires the proportional hazard assumption, ie, hazard ratio $\Theta_{qIRV}(t)/\ \Theta_{QIV}(t)$ does not depend on t, but is constant Θ. This assumption is reasonable for a seasonal infectious disease.

A Cox regression model with the study intervention as a covariate will be fit for each age group (18 through 64 years of age, ≥65 years of age), separately.

For the time-to-event analysis, the time in the analysis will be the number of days from 14 days after vaccination to the first event for participants with confirmed influenza. Participants without confirmed influenza (eg, first-episode LCI case with associated per-protocol ILI, caused by any strain) will be censored at the end of the influenza season or at the data cutoff date for performing primary efficacy analysis, at the last successful contact, death, or discontinuation from the study. For these censored participants, the time for analysis will be calculated, in days, from 14 days after vaccination until censoring time.

In addition, a Cox regression model may be fit for each age group (18 through 64 years of age and ≥65 years of age) with the study intervention as a covariate, and the influenza season (northern hemisphere 2022-2023 and southern hemisphere 2023) as a stratification factor.

5.2.3.3. Case Accrual Plot

The plot for the estimated cumulative number of cases/attack rate/incidence rate of first laboratory-confirmed influenza, caused by any influenza viral types/subtypes, associated with the occurrence of a protocol-defined ILI over time (days since vaccination), by study intervention, for each group (18 through 64 years of age, ≥65 years of age), separately, will be produced.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

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

5.3.1.1. Reactogenicity Data

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

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

The reactogenicity data are collected through the reactogenicity e-diary, which does not allow participants to skip a question. Therefore, for a specific day, if the e-diary data are transferred for that day, all the reactogenicity data for the participant on that day are nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.1.2.1 and Section 3.1.2.2.

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

5.3.2. Immunogenicity Data

Any assay results above the LLOQ are considered accurate, and their quantitated values will be reported. Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to CCI for GMT analysis. If the LLOQ is missing and the LOD is available for either serum or CCI data, the LOD will be used for LLOQ.

No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

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

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

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

5.3.3. Efficacy Data

Participants who discontinued from the study because of either loss to follow-up or death will be assumed to have no cases after the discontinuation for the analysis of efficacy-related endpoints.

Missing laboratory results such as "indeterminate," "QNS," or "not done" from the PCR test will be considered CCI when used to determine CCI. This approach will decrease the sensitivity of case detection and would only underestimate the VE. No other sensitivity analysis is planned.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. First-Episode LCI Cases With Associated Per-Protocol ILI in Participants 18 Through 64 Years of Age and in Participants ≥65 Years of Age

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.1).
- Analysis set: Evaluable efficacy population (Section 4).
- Analysis timing: At the time of sufficient case accrual in either age group or final analysis when the influenza season ends.
- Analysis methodology: RVE is calculated with 1 - risk ratio and will be expressed as a percentage. The risk ratio is the total number of first-episode LCI cases in the qIRV group compared to that in the QIV group. The CI of the RVE will use the conditional exact test based on the binomial distribution of the number of cases in the qIRV group, given the total number of cases in both groups, as specified in Section 5.2.3.1.
- Intercurrent events and missing data: Data collected after an intercurrent event will not be included. Missing data will not be imputed (Section 5.3.3).
- Reporting results:
    - The sample size, total number of first-episode LCI cases, and proportion of participants with LCI cases will be presented for each study intervention by age group (18 through 64 years of age, ≥65 years of age).
    - The estimated RVE and 95% CI for the VE using the exact method will be presented (Section 5.2.3.1).
    - A case accrual curve will be plotted by age group (18 through 64 years of age, ≥65 years of age).
    - RVE over time (by Months 1, 2, 3, etc, after vaccination) will be plotted by age group.

6.1.1.2. Sensitivity/Supplementary Analysis

To support the assessment of RVE, an analysis of the primary efficacy endpoint will be performed by adjusting for person-time through the Poisson regression and Cox regression[5] models Section 5.2.3.2. An additional analysis of the primary efficacy endpoint using a treatment policy estimand strategy will be performed by age group. It will use the same methodology and summary as the main analysis, but observations that occur after the intercurrent events of study withdrawal or important protocol deviation will be included.

6.1.2. Local Reactions and Systemic Events

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Reactogenicity e-diary safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting each event, using the Clopper-Pearson method (Section 5.2.1).
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis at that vaccination; for participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
  Partially missing e-diary data are imputed as "no" (Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.
- Analysis timing: Day 1 through Day 7 after vaccination.
- Reporting results:
  - Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented, by each study intervention group, for each age group (18 through 64 years of age, ≥65 years of age).
  - Bar charts with the proportions of participants for each and any local reaction, and each and any systemic event, through the 7 days following vaccination will be plotted, by each study intervention group, for each age group (18 through 64 years of age, ≥65 years of age). The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.2.2. Sensitivity/Supplementary Analyses

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.2.1 and Section 3.1.2.2, will be summarized with the same analysis time point and analysis population:

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

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

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

In addition, the proportions of participants reporting prompted local reactions and systemic events by maximum severity level with any e-diary errors will be included as a supplemental summary.

6.1.3. AEs and SAEs

6.1.3.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting those events, using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: Day 1 through 4 weeks after vaccination for AEs; Day 1 through 6 months after vaccination for SAEs.
- Intercurrent events and missing data: All data collected are included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Reporting results:
    - The number of participants with AEs through 4 weeks after vaccination (n), proportion (%), and associated 2-sided Clopper-Pearson 95% CI, will be presented by each study intervention group, separately, for each analysis interval (Section 3.1.2.4), and for each age group (18 through 64 years of age, ≥65 years of age), and overall.
    - The number of participants with SAEs through 6 months after vaccination (n), proportion (%), and associated 2-sided Clopper-Pearson 95% CI will be presented by each study intervention group, separately, for each analysis interval (Section 3.1.2.5), and for each age group (18 through 64 years of age, ≥65 years of age), and overall.
    - Descriptive statistics, including the proportion (%), the numerator (n) and the denominator used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method, will be presented, by each SOC and PT within each SOC, by study intervention group for each age group (18 through 64 years of age, ≥65 years of age), and overall.

6.1.3.2. Sensitivity/Supplementary Analysis

To support the assessment of AEs, the endpoints below as specified in Section 3.1.2.4 and Section 3.1.2.5 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

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

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

In addition, any AEs occurring up to 48 hours after blood draws or collection of midturbinate swabs will be listed separately.

6.2. Secondary Endpoint(s)

6.2.1. Immunogenicity Measured by HAI Titers

6.2.1.1. Main Analysis

The antibody titers measured by HAI assays CCI [redacted] will be analyzed separately. The analysis of antibody titers based on the HAI assay CCI [redacted] will have the following attributes. The analysis of the antibody titers based on the HAI assay CCI [redacted] will have the same attributes but will be based on the evaluable immunogenicity population (HAI assays CCI [redacted].

- Estimand strategy: Hypothetical approach (Section 2.2.3).
- Analysis set: Evaluable immunogenicity population (HAI assays CCI [redacted]) (Section 4).
- Analysis methodology: Calculation of GMR and difference in seroconversion, as well as descriptive summary statistics (Section 5.2.1 and Section 5.2.2).
- Analysis timing: Day 1, 4 weeks after study intervention.

- Intercurrent events and missing data: All data collected after or at intercurrent events will be excluded. Antibody titers data will be handled as described in Section 5.3.2. Missing data will not be imputed.

- Reporting results:

  - GMRs for each strain in qIRV recipients compared to QIV recipients, and associated 2-sided 95% CIs, will be presented 4 weeks after study intervention, separately, for each age group (18 through 64 years of age, ≥65 years of age) in the northern hemisphere.

  - The difference in percentage of participants achieving seroconversion for each strain 4 weeks after vaccination in qIRV recipients compared to QIV recipients, and associated 2-sided 95% CIs, will be provided, separately, by age group (18 through 64 years of age, ≥65 years of age) in the northern hemisphere.

  - Descriptive statistics, including the sample size (n), GMTs, GMFRs, and 95% CI for the GMTs and GMFRs, will be presented, by study intervention (Section 5.2.2) and strain, separately, for each age group in the northern hemisphere and southern hemisphere, respectively.

  - The proportion of participants with HAI titers ≥1:40 for each strain before vaccination and at each time point after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided, by study intervention, separately, for each age group (18 through 64 years of age, ≥65 years of age) in the northern hemisphere and southern hemisphere, respectively.

  - Empirical RCDCs will be plotted, by study intervention, separately, for each age group (18 through 64 years of age, ≥65 years of age) in the northern hemisphere and southern hemisphere, respectively.

  - The proportion of participants achieving HAI seroconversion 4 weeks after study intervention for each strain, and the associated 95% CIs, will be provided, by study intervention, separately, for each age group (18 through 64 years of age, ≥65 years of age) in the northern hemisphere and southern hemisphere, respectively.

  - The pooled immunogenicity analysis (eg, GMT, GMFR, proportion of participants with HAI titers ≥1:40, proportion of participants achieving HAI seroconversion) may be done for each common strain in both northern hemisphere and southern hemisphere influenza seasons.

6.2.1.2. Sensitivity/Supplementary Analysis

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

6.2.2. First-Episode CCI or LCI Cases With Different Definitions of ILI

All or selected analyses and data presentation for the primary endpoint (Section 6.1.1) will be repeated for following secondary efficacy endpoints by each group (18 through 64 years of age and ≥65 years of age), separately.

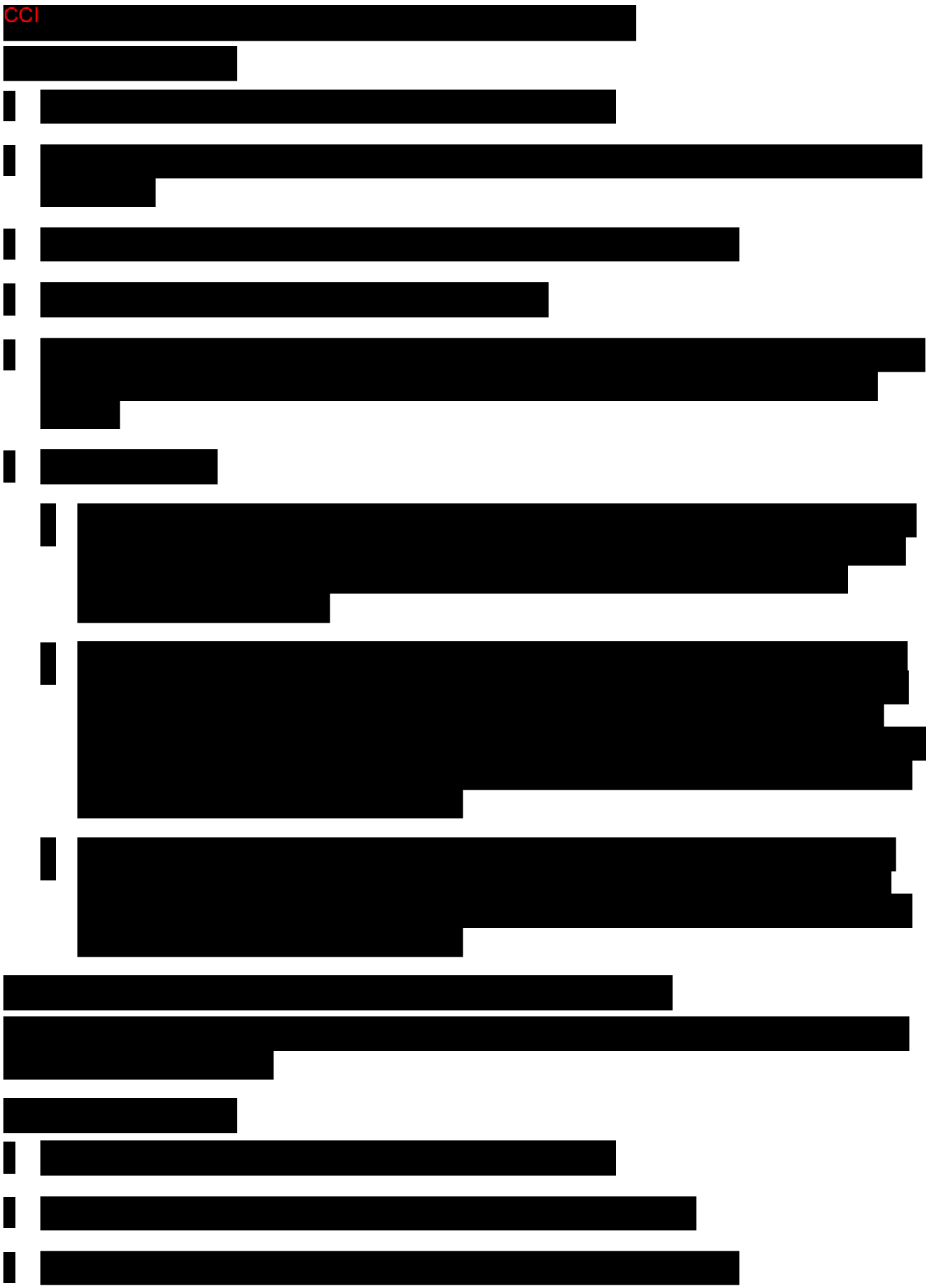
- First-episode LCI cases with associated per-protocol ILI, caused by all matched strains.
- First-episode LCI cases with associated per-protocol ILI, caused by each matched strain.
- First-episode LCI cases with associated per-protocol ILI, caused by unmatched strains.
- First-episode CCI cases with associated per-protocol ILI, caused by any strain.
- First-episode LCI associated with ILI, as defined by applying a modified CDC definition, caused by any strain.
- First-episode LCI cases associated with ILI, as defined by applying the WHO definition, caused by any strain.
- First-episode cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI.

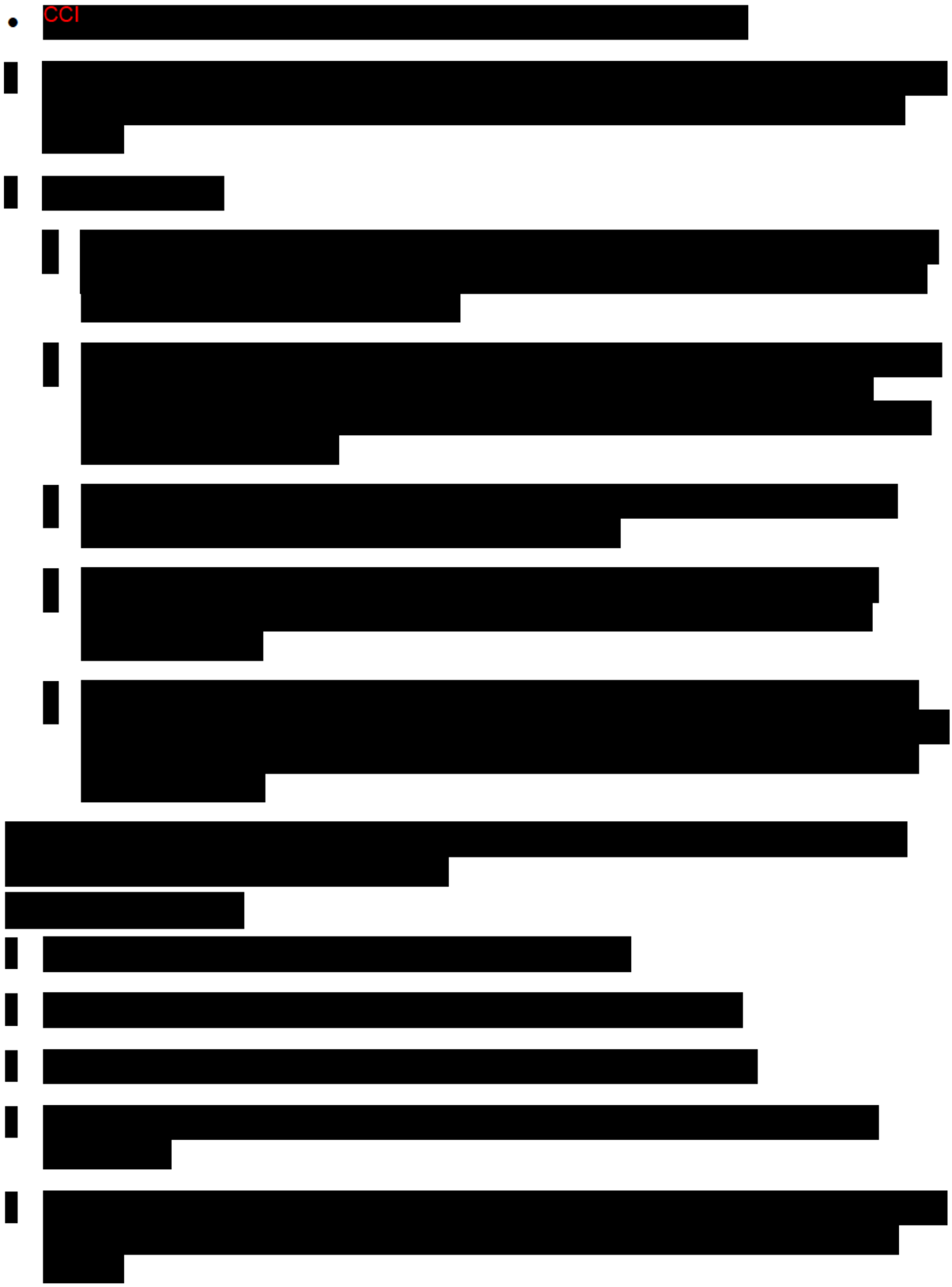
6.3. Other/Exploratory Endpoint(s)

CCI

[redacted]

CCI





- CCI [redacted]

- CCI [redacted]

6.4. Subset Analyses

Selected efficacy endpoints, immunogenicity endpoints, local reactions, systemic events, and AEs/SAEs will be analyzed by the following categories:

- Age group (18-49 years of age, 50-64 years of age, 65-74 years of age, 75 years of age or older),
- Sex,
- Race,
- Ethnicity, and
- Influenza virus type.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics and Medical History

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

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

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

All randomized participants will be included in the disposition summaries. Summaries will be displayed by study intervention, separately, for each age group (18 through 64 years of age, ≥65 years of age).

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the number and percentage of participants who received vaccinations, completed the follow-up visits, and withdrew before each follow-up visit phase, along with the reasons for withdrawal, will be tabulated by study intervention group and the total sample for each age group (18 through 64 years of age, ≥65 years of age). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized, separately, by study intervention group, along with the reasons for exclusion by study intervention for each age group (18 through 64 years of age, ≥65 years of age).

A listing of protocol deviations may also be provided.

6.5.2.2. Blood Samples for Assay

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

6.5.2.3. E-Diaries

The participants who were vaccinated and who transmitted and completed their e-diaries, as defined in Section 3.4.2, will be summarized according to the vaccine received for each age group (18 to 64 years of age, ≥65 years of age). The summary will also include the number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and completing the e-diary for any day in the required reporting period, by assigned study intervention, for each age group.

The number and percentage of participants transmitting and completing the e-diary for each day and all days (Day 1 to Day 7) in the required reporting period will be tabulated for each study intervention, by each age group (18 through 64 years of age, ≥65 years of age).

The reactogenicity e-diary safety population will be used.

6.5.3. Study Intervention Exposure

6.5.3.1. Vaccination Timing and Administration

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

A listing of participants showing the randomized study vaccine and the study vaccine received will be presented, by each age group.

6.5.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine collected during a scheduled study visit will be summarized according to the ATC fourth-level classification by age group (18 through 64 years of age, ≥65 years of age). The prior/concomitant vaccine received before vaccination will be listed. The number and percentage of randomized participants receiving each concomitant vaccine after study intervention will be tabulated, by age group (18 through 64 years of age, ≥65 years of age), according to the assigned study intervention. The concomitant medications will be summarized in a similar way as concomitant vaccines.

In addition, the number and percentage of participants using any nondrug treatment from ILI visits will be summarized, by age group (18 through 64 years of age, ≥65 years of age). The nondrug treatment collected (eg, mechanical ventilation use, oxygen use) to treat ILI symptoms will be summarized in a similar way.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers (Section 3.5.1). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the active vaccine and seasonal QIV groups in the percentage of participants reporting the events based on the Miettinen and Nurminen[3] method will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. AE displays will be sorted in descending order of point estimates of risk difference within SOC.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

Local reaction, systemic event, AE, and SAE summaries are described under Section 6.1.2 and Section 6.1.3.

The summary of differences in the frequencies of solicited local reactions and systemic events will be provided between 2 methods: summary with e-diary data only, and summary with e-diary data combining with reactogenicity data from the AE CRF.

A listing will be generated by age group (18 through 64 years of age, ≥65 years of age) for all the participants with unscheduled/unplanned visits because of severe (Grade 3) or suspected Grade 4 reactions.

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

The descriptive summary statistics for participants with at-risk comorbidities (total number and percentage) will be presented, by study intervention, for each age group (18 through 64 years of age, ≥65 years of age) and overall.

In addition, any symptom(s) that might be indicative of myocarditis or pericarditis within 14 days after a study vaccination (ECG, troponin level, and, if warranted, further cardiac evaluation with cardiac echocardiogram and/or cardiac magnetic resonance study) will be listed and/or summarized, by study intervention, for each age group (18 through 64 years of age, ≥65 years of age).

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis is planned for this study.

7.2. Data Monitoring Committee

This study will use an EDMC. The EDMC is independent of the study team and includes only external members. The EDMC charter describes the role of the EDMC in more detail.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC 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 endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

7.3. Analysis Timings

Primary analysis for the younger age stratum (participants 18 through 64 years of age): Analysis of the primary efficacy and immunogenicity objectives will be conducted when at least CCI first-episode evaluable LCI cases associated with per-protocol ILI caused by any strain have been accrued.

Final analysis for the younger age stratum (participants 18 through 64 years of age): Analysis of the efficacy, safety, and immunogenicity objectives will be performed following completion of the last visit of the last participant in the study. Other efficacy, safety, and immunogenicity analyses may be performed between the primary efficacy and final analyses.

Primary analysis for the older age stratum (participants ≥65 years of age): Analysis of the primary efficacy, safety, and immunogenicity objectives may be conducted when at least CCI first-episode valuable LCI cases associated with per-protocol ILI caused by any strain have been accrued.

All VE estimations with any additional LCI cases collected after primary analysis for each age stratum will be descriptively summarized.

Complete safety, immunogenicity, and efficacy analysis will be performed at the end of the study.

8. REFERENCES

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APPENDICES

Appendix 1. Summary of Efficacy Analyses

The following table is an overview of VE analyses for primary, secondary, and exploratory efficacy endpoints. The similar analyses will be repeated for each subgroup of age (18-49 years of age, 50-64 years of age, 65-74 years of age, 75 years of age or older), sex, race, ethnicity, and influenza virus type separately.

Objective	Endpoint	Analysis Type	Population	Statistical Method/ Analysis Model
Primary	First-episode LCI cases with associated per-protocol ILI, caused by any strain	Main analysis	Evaluable (18 through 64 years of age)	Binomial
		Sensitivity/ supplementary analysis	Evaluable (18 through 64 years of age)	Poisson regression, Cox regression
		Sensitivity/ supplementary analysis	mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression
	First-episode LCI cases with associated per-protocol ILI, caused by any strain	Main analysis	Evaluable (≥65 years of age)	Binomial
		Sensitivity/ supplementary analysis	Evaluable (≥65 years of age)	Poisson regression, Cox regression
		Sensitivity/ supplementary analysis	mITT (≥65 years of age)	Binomial, Poisson regression, Cox regression
Secondary	First-episode LCI cases with associated per-protocol ILI, caused by all matched strains		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age), mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression
	First-episode LCI cases with associated per-protocol ILI, caused by each matched strain		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age), mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression

Objective	Endpoint	Analysis Type	Population	Statistical Method/ Analysis Model
	First-episode LCI cases with associated per-protocol ILI, caused by all unmatched strains		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age), mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression
	First-episode CCI cases with associated per-protocol ILI, caused by any strain		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age) mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression
	First-episode LCI associated with ILI, as defined by applying a modified CDC definition, caused by any strain		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age), mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression
	First-episode LCI cases associated with ILI, as defined by applying the WHO definition, caused by any strain		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age), mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression
	First-episode cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI		Evaluable (≥65 years of age), Evaluable (18 through 64 years of age), mITT (≥65 years of age), mITT (18 through 64 years of age)	Binomial, Poisson regression, Cox regression

Objective	Endpoint	Analysis Type	Population	Statistical Method/ Analysis Model
CCI				

Objective	Endpoint	Analysis Type	Population	Statistical Method/ Analysis Model
CCI [redacted]				

Appendix 2. Data Derivation Details

Appendix 2.1. Efficacy Endpoint Derivations

1. First-episode LCI cases with associated per-protocol ILI, caused by any strain.

CCI

2. First-episode CCI cases with associated per-protocol ILI, caused by any strain.

   The flowchart is similar to that in No. 1 above, except influenza infection is confirmed through culture at a central laboratory.

3. First-episode LCI associated with ILI, as defined by applying a modified CDC definition, caused by any strain.

   The flowchart is similar to that in No. 1 above, except respiratory symptoms and systemic symptoms are revised as following:

   Respiratory symptoms:

   - Sore throat or
   - Cough

   Systemic symptom:

   - Oral temperature of >37.2°C (>99.0°F)

4. First-episode LCI cases associated with ILI, as defined by applying the WHO definition, caused by any strain.

   The flowchart is similar to that in No. 1 above, except respiratory symptoms and systemic symptoms are revised as following:

   Respiratory symptom:

   - Cough

   Systemic symptom:

   - Oral temperature ≥38.0°C (≥100.4°F)

5. First-episode cases of influenza, as confirmed by central or local RT-PCR or culture, with associated per-protocol ILI.

   The flowchart is similar to that in No. 1 above, except cases with influenza infection confirmed through RT-PCR culture at a local laboratory are also included.

6. Follow-up time derivation.

   The start time of surveillance will be 14 days after vaccination (ie, Day 15). There will be no follow-up time for participants who are completely excluded from the evaluable efficacy population. If participants are excluded from the study after some time after the important protocol deviation from the evaluable efficacy population, the stop date of the follow-up time will be the time of the important protocol deviation.

   Sensitivity analysis for CCI [redacted] will follow similar rules to that stated in the above paragraph.

   First-episode severe (severe influenza) LCI cases with associated per-protocol ILI caused by any strain are above first-episode LCI cases hospitalized for ILI.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AMT	antigenic match test
APE	analysis population exclusion
ATC	Anatomic Therapeutic Chemical
BLQ	below the limit of quantitation
BMI	body mass index
CCI	culture-confirmed influenza
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CORD	clinical oversight review dashboard
COVID-19	coronavirus disease 2019
CRF	case report form
ECG	electrocardiogram
e-diary	electronic diary
EDMC	external data monitoring committee
ER	emergency room
FDA	Food and Drug Administration (United States)
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutinin inhibition assay
ICD	informed consent document
ICU	intensive care unit
ILI	influenza-like illness
IPM	investigational product manual
IRR	incidence rate ratio
IV	intravenous(ly)
IWRS	interactive Web-based response system
LCI	laboratory-confirmed influenza
LLOQ	lower limit of quantitation
LOD	limit of detection
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
CCI [redacted]	
modRNA	nucleoside-modified messenger ribonucleic acid
N/A	not applicable
NEG	negative
CCI [redacted]	

Abbreviation	Term
PCR	polymerase chain reaction
PIPD	potentially important protocol deviations
POS	positive
PP	per-protocol
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RR	relative risk
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
RVE	relative vaccine efficacy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
VE	vaccine efficacy
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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Signed By:	Date(GMT)	Signing Capacity
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